Additive Manufacturing for Biomedical Implants and Prosthetics

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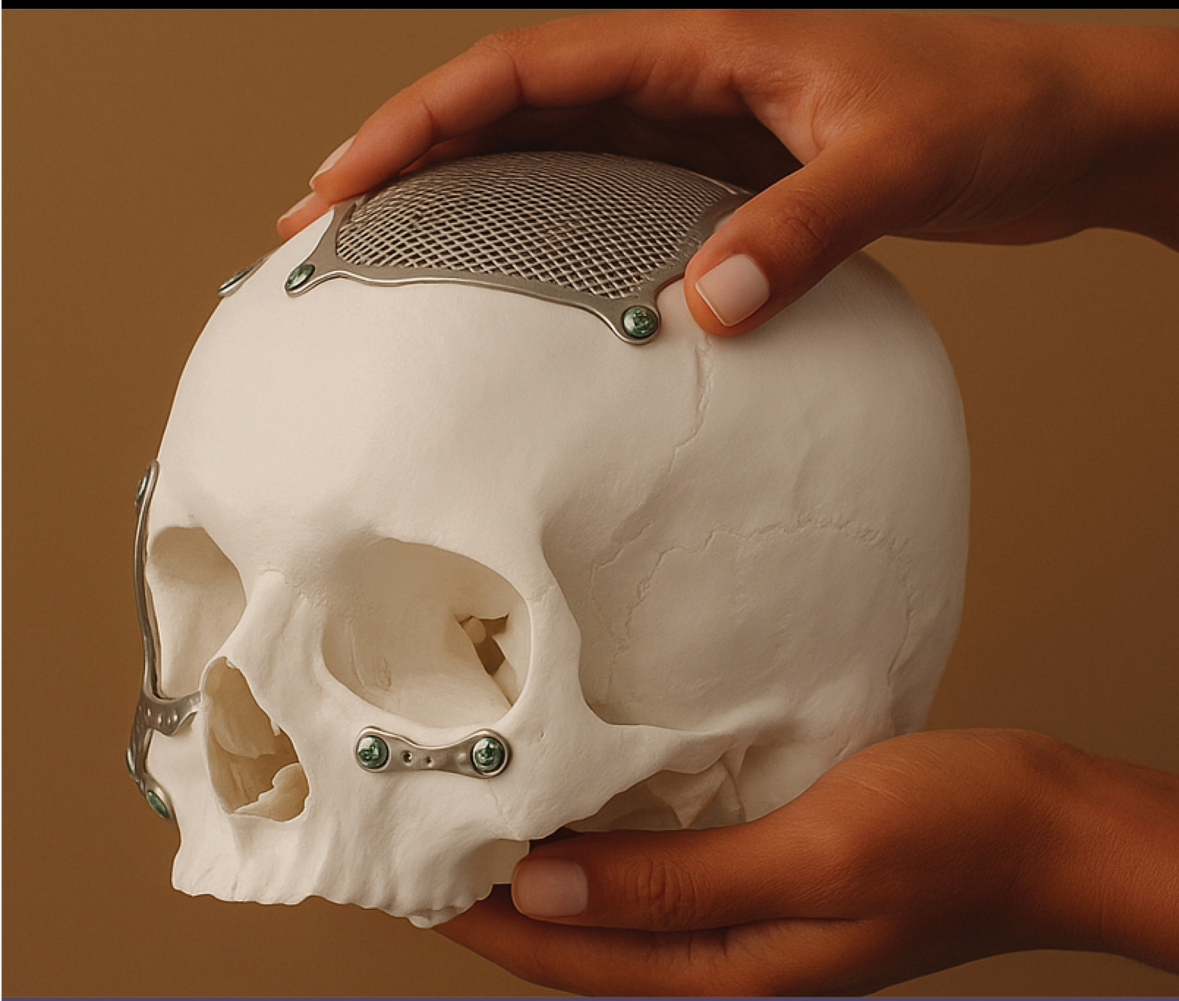

Edited by Pawan Kumar Rakesh and Pravin Kumar

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Additive Manufacturing for Biomedical Implants and Prosthetics

This book explains usage of additive manufacturing (AM) for the printing of biomedical implants and prosthetics. It elaborates on the basics of printing biomedical implants and prosthetics, including necessity, printing processes, materials, and standards followed by discussion of involved technologies, design and optimization, and post-processing. It further highlights patient response and risks of biomedical implants, including future scope. Sustainability and environmental concerns while AM of implants and process optimization are also covered.

Book highlights

- Provides wide coverage of the contents related to additive manufacturing (AM) of bio-implants and prosthetics
- Details fabrication details, properties, and features of fabricated implants, their testing, and characterization
- Discusses environmental issues and optimization
- Covers economic implications of AM in biomedical industry
- Includes dedicated chapters on Industry 4.0 interventions and sustainability

This book is aimed at graduate students and researchers in bioengineering, materials science, implant design, and fabrication.

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Pawan Kumar Rakesh and Pravin Kumar

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Preface

The field of additive manufacturing (AM) has revolutionized numerous industries, and its impact on biomedical implants and prosthetics is particularly transformative. The advent of advanced 3D printing technologies has enabled the creation of customized, patient-specific implants and prosthetics that offer improved performance, functionality, and comfort compared to traditional methods. This book, "Additive Manufacturing for Biomedical Implants and Prosthetics", serves as a comprehensive guide to the advancements, challenges, and future trends of AM in the biomedical domain. The main objective of this book is to bridge the knowledge gap between the evolving field of AM and its applications in healthcare. It provides in-depth coverage of how 3D printing technologies are utilized to create next-generation implants and prosthetics that cater to the specific needs of individual patients.

This book delves into various aspects of AM for biomedical applications, including the materials used, design considerations, fabrication techniques, and post-processing requirements. The book also discusses regulatory challenges, biocompatibility issues, and the ethical implications of producing personalized medical devices through AM. This book is intended for a wide audience, including researchers, engineers, healthcare professionals, and students working in the fields of biomedical engineering, materials science, and medical device design. The advancements in AM hold the potential to transform healthcare delivery and significantly improve the quality of life for individuals in need of customized implants and prosthetics.

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Dr. Rakesh has supervised four PhD and six M.Tech. students and was honored with the Best Faculty Award in 2023.

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Introduction

The convergence of biocompatible materials and additive manufacturing technologies has revolutionized the field of modern restoration and rehabilitation, addressing needs from skin repair to bone replacement. This book represents a pivotal contribution to the field by exploring the use of additive manufacturing for biomedical implants and prosthetics. Comprising 11 comprehensive chapters, it offers valuable insights for readers from diverse backgrounds.

Chapter 1 introduces the fundamentals of additive manufacturing for biomedical implants and prosthetics, covering the necessity, key printing processes, and materials involved. The technology's advantages, such as near-net-shape production, reduced material wastage, and faster time-to-market, are highlighted. Chapter 2 focuses on pre- and post-processing techniques for orthopedic implants. Preprocessing involves selecting biocompatible materials, optimizing designs, and conducting finite element analyses to reduce material waste while ensuring mechanical integrity and patient-specific customization. Post-processing includes essential procedures like cleaning and surface finishing enhancing structural integrity and mitigating adverse biological reactions.

Chapter 3 delves into biomedical standards and regulations, comparing pathways for mass-produced and custom-made implants and prosthetic devices. It emphasizes how national regulatory bodies ensure safety and performance through established standards. Chapter 4 explores the materials used in fabricating personalized implantable prosthetics, detailing the evolution of 3D printing in medical applications such as orthopedics, neurosurgery, dentistry, and reconstructive surgery. Additive manufacturing techniques like laser powder bed fusion, electron beam melting, and stereolithography are shown to facilitate the creation of patient-specific structures.

In Chapter 5, the focus is on 3D-printed scaffolds for tissue engineering, highlighting their ability to provide controlled porosity, mechanical properties, and interconnectivity to support cell attachment, proliferation, and differentiation. The incorporation of bioactive molecules such as growth factors further enhances tissue regeneration. Chapter 6 examines the mechanical and tribological properties of polymethylmethacrylate (PMMA)-based dental biocomposites. It categorizes these composites into various types—PMMA with organic polymers, metal nanoparticles, graphene, carbon nanotubes, and calcium phosphate—and reviews their applications and research advancements in dentistry.

Chapter 7 addresses the fabrication of prosthetic feet using biocomposites through additive manufacturing. These biocomposites, made from natural fibers and biodegradable polymers like polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA), and poly(p-dioxanone) (PDS), offer benefits such as non-toxicity, renewability, and degradability, making them ideal for prosthetic applications.

Chapter 8 explores technologies that support additive manufacturing in biomedical applications. This includes bio-printing, tissue engineering, disease modeling, patient-specific implants, drug delivery systems, and virtual surgical planning. The chapter also discusses bio-inks and materials used for cell-seeded tissues, implants,

and organ scaffolds, underscoring additive manufacturing's role in enhancing safety, innovation, and convenience in healthcare.

Chapter 9 provides insights into additive manufacturing technologies for biomedical applications, focusing on customized prosthetics, implants, and surgical tools. Advances in high-resolution imaging techniques like CT and MRI are highlighted for their role in creating precise anatomical models and personalized medical devices. Chapter 10 examines how Industry 4.0 technologies are integrating with additive manufacturing to transform the production of complex, patient-specific prosthetics, implants, and medical devices. This chapter reviews the benefits, limitations, and applications of Industry 4.0 in the biomedical sector.

Finally, Chapter 11 evaluates the economic impact of additive manufacturing technologies, discussing their potential to reshape the healthcare supply chain, reduce costs, and enhance patient-specific solutions. The chapter examines equipment, materials, and operational expenses, emphasizing how material efficiency can minimize waste and improve cost-effectiveness.

1 Implementation of Additive Manufacturing in Biomedical

Bhanupratap Gaur and Bharti Dhaundiyal

1.1 INTRODUCTION TO ADDITIVE MANUFACTURING IN BIOMEDICAL APPLICATIONS

1.1.1 History and Evolution of AM in Biomedicine

Historic development of additive manufacturing (AM) was initiated in the 1950s and 1960s but gained pace in the 1980s due to the advent of associated technologies and patent filings [1]. Back then in the 1980s, it was conceived as a tool for rapid prototyping [2]. Its inception marked a departure from traditional manufacturing techniques, offering a layer-by-layer approach to object creation was revolutionary. Early applications of AM were primarily focused on industrial design and manufacturing, where it allowed for the rapid production of models and parts directly from computer-aided design (CAD) data, significantly reducing the development time for new products [1].

As AM technology evolved, its versatility quickly became apparent. Its potential beyond prototyping and industrial applications began to be realized [3]. The development of materials compatible with AM processes expanded its applicability, paving the way for its entry into more varied and impactful fields. This progression from simple plastic models to the production of functional metal and ceramic parts marked a pivotal shift, setting the stage for AM's transformative impact on biomedical applications [4]. The transition into biomedicine was facilitated by advancements in material science and the advent of biocompatible materials, enabling the production of custom medical devices and implants, thus beginning its profound influence on healthcare [5].

1.1.2 Scope of AM in Biomedical Applications

The scope of AM in the biomedical domain is vast and multidimensional. It extends from the production of custom prosthetics and orthopedic implants to the fabrication of dental restorations and beyond [6]. AM's ability to produce highly complex structures has made it a cornerstone in personalized medicine, where patient-specific solutions are paramount. This technology enables the creation of implants that perfectly fit the patient's anatomy, significantly improving the outcomes of surgical treatments [6].

Beyond structural implants, AM's versatility allows for the development of surgical instruments tailored to specific procedures or patient needs, enhancing surgical

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efficiency and safety. Furthermore, AM has produced anatomical models from patient imaging data. These models are invaluable for surgical planning and education, providing a tangible reference that improves the understanding of complex anatomical scenarios [7].

One of the most promising areas of AM in biomedicine is tissue engineering, where scaffolds are created to support the growth of new tissues for regenerative medicine [8]. These scaffolds can be designed with intricate geometries and porosities that mimic the natural environment, promoting cell growth and tissue regeneration [9]. The scope of AM in biomedicine includes the bioprinting of organs and tissues, offering a potential solution to the shortage of organ donors. This technology is poised to revolutionize transplant medicine by enabling the production of organs tailored to the patient's immune profile, thereby reducing the risks of rejection and complications [10]. AM heralds a new era in personalized medicine, particularly in drug delivery. It enables the precise fabrication of dosage forms with customizable release profiles, tailored to meet individual patient needs. This innovation ensures optimal therapeutic outcomes, significantly enhancing patient compliance and the effectiveness of treatments. AM's role in personalized drug delivery exemplifies its transformative impact on healthcare [11].

In summary, AM's scope in biomedical applications encompasses the customization of medical devices, the innovation of surgical tools, the advancement of regenerative medicine, and the potential transformation of organ transplantation, marking it as a pivotal technology in the evolution of healthcare.

1.2 ANATOMICAL MODELS AND BONE RESECTION JIGS

1.2.1 Introduction to Anatomical Models and Bone Resection Jigs

Anatomical models and bone resection jigs, fabricated using AM, represent a significant advancement in the planning and execution of complex surgical procedures. Anatomical models are precise, patient-specific replicas made from medical imaging data, such as computed tomography (CT) scans or magnetic resonance imagings (MRIs) [12]. These models provide a physical representation of patient anatomy that is invaluable for surgical planning, training, and mock surgery, as represented in Figure 1.1(a). They allow surgeons to deeply understand unique anatomical complexities before an operation, enhancing surgical precision and confidence.

Bone resection jigs, on the other hand, are custom-made templates used during surgeries to ensure the accurate cutting of bones, as represented in Figure 1.1(b). These jigs are designed based on the specific dimensions and contours of a patient's anatomy, ensuring cuts are made precisely where needed. This is particularly vital in orthopedic surgery, such as joint replacements and bone reconstructions, where precise alignment and placement of implants are critical for the success of the surgery [13].

The use of AM in creating these tools is revolutionary. It allows for rapid prototyping and production, enabling a quick turnaround from imaging to surgical application. This integration of AM into medical practice not only streamlines surgical workflows but also minimizes risks associated with invasive procedures, ultimately leading to better patient outcomes [14].

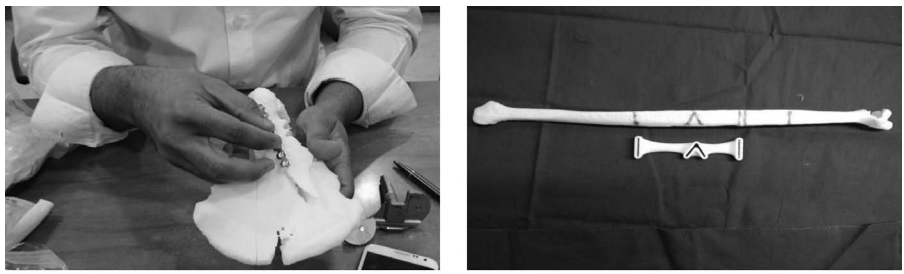

FIGURE 1.1 (a) A surgeon planning and carrying out a mock surgery by bending a reconstruction plate onto an additively manufactured plastic bone model; (b) Additively manufactured plastic fibula bone model and bone resection jig for cutting the model.

Photograph by the author.

1.2.2 Designing and Manufacturing

The design and manufacturing process of anatomical models and bone resection jigs using AM involves several critical steps. First, patient data from imaging techniques like CT or MRI scans is converted into a digital 3D model; see Figure 1.2(a)–(f)). This model is then refined using CAD software to create a blueprint for the anatomical model or jig. Attention to detail is crucial in this phase to ensure the accuracy of the final product.

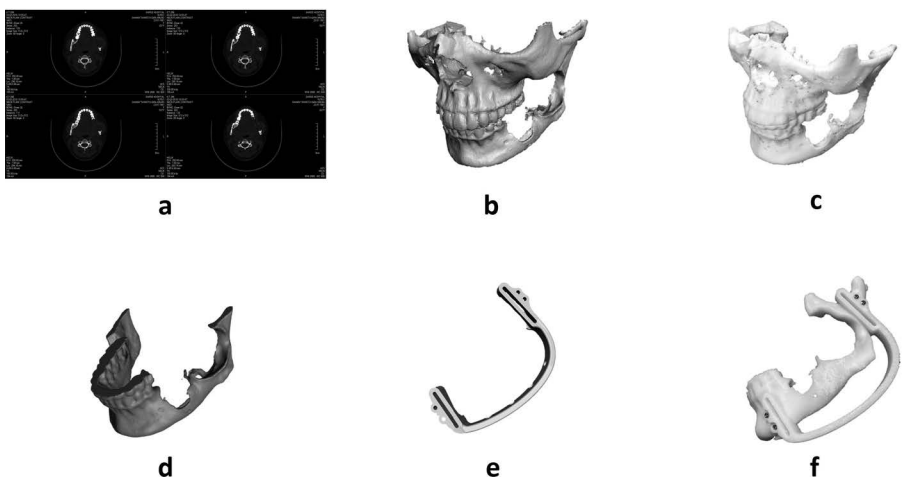

FIGURE 1.2 (a) CT image of maxillofacial region; (b) Virtual/CAD model of the facial bone; (c) Plastic AM model of the bone; (d) CAD model of mandible with a tumor that is to be cut; (e) CAD of bone resection jig designed using mandible CAD model shown in (d); (f) Bone resection jig placed on AM bone model, indicating their mutual position during bone cutting.

Photograph by the author.

Once the design is finalized, it is sent to an AM printer where the object is built layer by layer with suitable materials. Materials used in the production of anatomical models and jigs vary based on the required durability and the level of detail needed. Typically, polymers are used for models due to their versatility and color variability, which can mimic different tissue densities [15]. Metals or durable polymers are used for jigs to ensure they withstand surgical use.

The manufacturing process also includes post-processing steps such as curing, cleaning, and sometimes sterilization, especially for jigs that will be used in sterile surgical environments. The ability of AM to use these materials and create geometrically complex structures quickly is what sets it apart in the medical field, allowing for both rapid prototyping and end-use production [12].

1.2.3 Outcomes and Benefits

The integration of AM into the production of anatomical models and bone resection jigs brings numerous benefits and positive outcomes. For one, it enhances presurgical planning. Surgeons can plan and rehearse complex procedures with a high degree of accuracy, reducing surgery times and improving safety. This preparation is particularly beneficial in teaching hospitals, where models serve as excellent tools for educational purposes, allowing trainees to explore and understand complex surgical scenarios hands-on [7].

Furthermore, the use of customized bone resection jigs during surgery ensures that bone cuts are precise, which is crucial for the optimal fitting and positioning of implants. This precision reduces the likelihood of complications and the need for subsequent corrective surgeries, thus improving overall patient outcomes. Improved accuracy in surgery also minimizes tissue damage and can lead to faster recovery times [16].

Economically, while the upfront cost of implementing AM technology may be significant, the long-term benefits, including reduced operation times, fewer complications, and decreased need for additional surgeries, contribute to cost savings for healthcare facilities. Moreover, the tailored approach enhances patient satisfaction and success rates, positioning AM as a transformative force in modern surgical practices.

1.3 PATIENT-SPECIFIC IMPLANTS

1.3.1 Introduction to Patient-Specific Implants

Standard biomedical implants come in predefined sizes and shapes, designed to fit a broad patient population but often lacking the precision needed for optimal outcomes. In contrast, patient-customized implants are tailored to fit the unique anatomical details of an individual, created using precise medical imaging and AM [17]. This customization ensures a perfect fit, enhances integration with the body, and improves functionality, leading to better surgical outcomes, faster recovery, and reduced risk of complications [18]. Custom implants particularly excel in complex cases where standard sizes cannot adequately address specific medical needs, thereby significantly improving patient satisfaction and overall treatment effectiveness.

Patient-specific implants represent a transformative advancement in medical technology, offering tailor-made solutions designed to fit the unique anatomical features of individual patients. These implants are primarily used in orthopedics, cranio-maxillofacial, and cardiovascular surgeries, where the precise anatomical fit is crucial for the success of the intervention [4]. AM, with its capability for high customization, plays a pivotal role in the development of these implants.

The concept of patient-specific implants arises from the need to address the limitations of standard implants, which may not fit all patients perfectly, leading to discomfort, suboptimal functionality, or even rejection [19]. By using AM, implants are designed and manufactured to match the patient's exact anatomical specifications derived from detailed medical scans like CT or MRI [20]. This ensures a perfect fit, better integration with the body, and improved functionality of the implants.

1.3.2 Designing and Manufacturing

The process of designing and manufacturing patient-specific implants begins with acquiring accurate 3D data from patient imaging. Advanced software is used to convert this data into a digital model that precisely represents the patient's anatomy. Implant designing is done and finite element analysis is performed to make sure it will sustain functional loads during day-to-day activities of the patient, as represented in Figure 1.3(a) and (b). Engineers and medical professionals work together to modify this model to design an implant that not only fits perfectly but also fulfills specific functional requirements of the surgery or replacement. This collaborative effort of engineers and clinicians for the development of implants is often termed cocreation [21].

Once the design is approved, the digital model is sent to an AM printer where the implant is constructed layer by layer. Materials used in the manufacturing process vary based on the required properties of the implant, such as strength, flexibility, and biocompatibility [22]. Common materials used in AM for biomedical implants include titanium and its alloys, due to their excellent strength, biocompatibility, and corrosion resistance [23]. Cobalt-chrome (Co-Cr) is commonly used in dental and orthopedic implants because of its high strength, temperature endurance, and wear

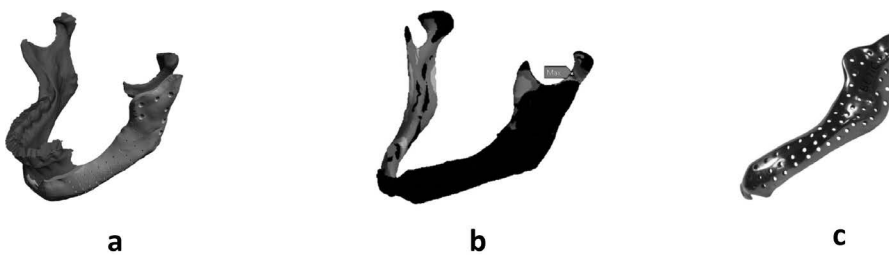

FIGURE 1.3 (a) Implant CAD model on mandible CAD model; (b) Implant FEA testing and design iterations; (c) Final implant after AM and post-processing.

Photograph by the author.

resistance [24]. Polymers like PEEKs (polyether ether ketones) are also popular for their lightweight properties and compatibility with medical imaging [25]. Stainless steel is used for its durability and mechanical properties, suitable for load-bearing implants [26]. Additionally, bioceramics, such as hydroxyapatite and tricalcium phosphate, are favored in bone implants for their osteoconductivity [27]. These materials can be tailored in AM processes to meet specific requirements, such as porosity and surface texture, enhancing their functionality and integration with human tissue.

Post-processing of metal implants created through AM is crucial for ensuring their safety, functionality, and compatibility with human tissue. This stage typically involves several steps: heat treatment, support removal, surface finishing, and sterilization [28]. Heat treatment is performed to relieve internal stresses and improve microstructure. Support structures used during the printing process are meticulously removed. Surface finishing, such as polishing or machining, is then applied to enhance the implant's surface quality; Figure 1.3(c) represents a finished implant after post-processing. Finally, sterilization ensures the implant is free from any contaminants before surgical implementation, critical for preventing infections and ensuring patient safety [29].

1.3.3 Impact and Advantages

The impact and advantages of patient-specific implants are significant across various aspects of healthcare and patient well-being. Clinically, these implants ensure improved alignment and integration with the patient's body, which reduces the risk of implant rejection and post-operative complications. This precision fit promotes faster healing and recovery, minimizing the patient's discomfort and downtime [19].

Functionally, patient-specific implants can restore the natural function of replaced parts more effectively than standard implants. This is particularly evident in joint replacements and dental implants, where a precise fit is essential for the natural movement and function. Additionally, the improved aesthetic outcomes in surgeries, such as craniofacial reconstructions, significantly enhance patient satisfaction and quality of life [4].

Scaffold or porous orthopedic implants, manufactured using AM, offer significant benefits for bone ingrowth and healing. The porous structure of these implants mimics natural bone architecture, promoting osteointegration where new bone cells grow into the pores, enhancing stability and longevity of the implant. This bioactive interface reduces the risk of implant rejection and accelerates the healing process. Additionally, the porous nature allows for reduced implant weight without sacrificing mechanical strength [30].

Economically, while the initial cost of patient-specific implants might be higher than off-the-shelf solutions, the reduction in surgical revisions, shorter hospital stays, and quicker recovery times contribute to overall cost-effectiveness in the long term. Moreover, the ability to plan surgeries with precise implants in hand reduces operation times and improves surgical outcomes, which is beneficial for both healthcare providers and patients. Overall, the use of AM in creating patient-specific implants exemplifies a leap forward in personalized medicine, offering tailored healthcare solutions that significantly enhance the efficacy and efficiency of medical treatments [31].

1.4 PROSTHETICS AND ORTHOTICS

1.4.1 Introduction to Prosthetics and Orthotics

Prosthetics and orthotics play a crucial role in rehabilitation, aiding individuals who have lost limbs or require support for body functions due to injury or congenital conditions. Prosthetics are artificial devices that replace missing body parts, while orthotics are supports or braces designed to correct or assist body posture and function [32]. The advent of AM in the biomedical field has revolutionized the design and production of these assistive devices, making them more accessible, affordable, and specifically tailored to individual needs.

Traditionally, prosthetics and orthotics were made using labor-intensive methods that could not always ensure a perfect fit, often leading to discomfort and suboptimal functionality. With AM, it is now possible to create devices that are fully customized to the wearer's anatomy, providing enhanced comfort and improved functionality [33]. The process begins with detailed scanning of the affected body part to gather precise measurements, followed by digital modeling that allows for exact replication and adjustment based on specific patient needs [32].

The use of AM in prosthetics and orthotics not only improves the physical fit but also allows for innovations in design that can integrate features such as lightweight, durable materials, and the incorporation of complex mechanical systems that mimic natural movement. This level of customization and functionality was unimaginable with traditional manufacturing techniques and marks a significant advancement in the field of rehabilitation technology [4].

1.4.2 Design and Customization through AM

The design and customization process of prosthetics and orthotics through AM offers unprecedented flexibility and precision. This process typically starts with capturing 3D data from the patient using scanning technologies. This data serves as the foundation for creating a digital model of the required device. Engineers and designers can manipulate this model to address very specific requirements and preferences, such as the device's weight, rigidity, and even aesthetic appearance [4].

In AM, the customization process is not only about size and fit but also involves optimizing the device's mechanical properties. For instance, in prosthetic limbs, different sections might need varying degrees of flexibility and strength to mimic natural movement accurately [34]. AM technologies such as Selective Laser Sintering (SLS) or Fused Deposition Modeling (FDM) allow for such gradations within a single build, creating zones with different material densities and characteristics, also known as functionally gradient products [35].

Moreover, AM facilitates the incorporation of user feedback into rapid prototypes, enabling iterative design enhancements that can be tested and refined in real time [36]. This iterative process ensures that the final product not only fits anatomically but also aligns with the functional needs and lifestyle of the user, potentially including personalized design touches that make the devices feel more personal and less medical.

1.4.3 Impact on Rehabilitation

The impact of using AM in the production of prosthetics and orthotics is profound in the field of rehabilitation. One of the most significant benefits is the improved speed and accessibility of device production. AM reduces the time from initial consultation to final delivery, which is crucial for patients who require immediate support or replacements. This rapid production capability also makes it feasible to update or replace devices as the patient's condition changes or improves, such as in the case of physical growth or recovery progression [33].

Functionally, the precise customization possible with AM results in devices that are much more comfortable and effective. A better-fitting prosthetic or orthotic leads to reduced physical discomfort and skin problems, often associated with poorly fitting devices. This comfort increases wear time, directly correlating with better rehabilitation outcomes [37].

Psychologically, the ability to design prosthetics that are aesthetically pleasing or match the wearer's body closely helps in enhancing self-esteem and social integration. Children, in particular, benefit from designs that can be personalized with colors and themes that appeal to them.

Economically, while the initial setup for AM might be costly, the long-term benefits of reduced waste, the ability to make alterations without starting from scratch, and decreased physical therapy due to better initial outcomes can lead to significant cost savings [38]. Overall, AM's role in prosthetics and orthotics marks a transformative shift toward more effective, personalized rehabilitation therapies.

1.5 TISSUE ENGINEERING AND REGENERATIVE MEDICINE

1.5.1 Introduction to Tissue Engineering

Tissue engineering is a revolutionary field within biomedical science that focuses on developing functional replacements for damaged or diseased tissues. This interdisciplinary field combines principles from biology, chemistry, engineering, and medicine to create biological substitutes that can restore, maintain, or improve tissue function [39]. Tissue engineering often involves the use of scaffolds, cells, and biologically active molecules to form new viable tissue for medical implants and supports the body's own repair mechanisms [40].

AM has emerged as a critical technology in tissue engineering, providing the precision and versatility needed to fabricate complex, three-dimensional structures that mimic the native environment for tissues. AM enables researchers to construct scaffolds that are not only biocompatible but also possess the necessary mechanical and structural properties to support cell attachment, proliferation, and differentiation [41]. The ultimate goal of tissue engineering is to overcome the limitations of traditional transplantations, such as donor scarcity and immune rejection, and to provide personalized medical solutions for regenerative medicine which seems promising through AM [42].

1.5.2 Scaffold Fabrication Using AM

In the realm of tissue engineering, scaffolds play a crucial role in providing a temporary physical matrix for cells to adhere, grow, and form new tissue. AM techniques are particularly suited to scaffold fabrication because they can precisely control the architecture of these structures at the micro and macro scale. AM allows for the design of scaffolds with specific porosity, geometry, and degradation rates, which are essential for mimicking the extracellular matrix and promoting tissue regeneration [43].

Materials used in AM for scaffolds include a range of biodegradable polymers, ceramics, hydrogels, and composites that can be processed under conditions that preserve their biocompatibility. Techniques such as stereolithography, SLS, and FDM are commonly used, each offering different advantages in terms of material compatibility and resolution [44]. The ability to incorporate gradients of biochemical cues and varying mechanical properties within a scaffold are also notable benefits of AM, facilitating the engineering of complex tissue structures such as vascularized organs, layered skin, or intervertebral discs [8].

Tissue printing using inkjet AM is a cutting-edge technique in regenerative medicine, focusing on the creation of complex, functional tissues. In this process, bioinks—comprising stem cells, growth factors, hormones, hydrogels, and nutrients—are precisely deposited layer by layer to form a scaffold made from materials like hydroxyapatite or gelatin [45]. These materials are chosen for their biocompatibility and structural properties, providing a matrix that supports cell attachment and growth. The printed structure then undergoes a maturation process in a controlled environment, allowing the cells to proliferate and differentiate into the desired tissue. This maturation is crucial for ensuring that the engineered organ develops the necessary biological and mechanical properties before being implanted into a patient [46]. This technology holds tremendous potential for personalized medicine, enabling the replacement of damaged tissues with fully functional, patient-specific counterparts.

1.5.3 Advancements and Breakthroughs

The advancements and breakthroughs in tissue engineering facilitated by AM are shaping a new era in regenerative medicine. One of the most significant breakthroughs has been the ability to create vascularized tissues, which are essential for the survival of engineered organs once implanted. AM techniques have enabled the fabrication of intricate vascular networks within scaffolds that mimic the body's natural blood supply systems, ensuring that cells receive the necessary nutrients and oxygen to survive [42].

Another advancement includes the development of "smart scaffolds," which are embedded with sensors that monitor the behavior and health of the cells and the developing tissue. These scaffolds can provide real-time feedback on the regenerative process, allowing for adjustments in treatment protocols to optimize outcomes [47]. Additionally, the integration of stem cell technology with AM scaffold fabrication opens up possibilities for creating more complex tissues and organs. Stem cells can be differentiated into a wide range of specific cell types, offering the potential for the full restoration of organ function [48].

Significant strides have been made in the field of organ printing, particularly with tissues such as skin, bladders, and vascular structures. For example, bioprinted skin has been successfully transplanted onto burn victims [49], and bladders bioprinted with patient-specific cells have been implanted with promising outcomes [50]. Meanwhile, ongoing research focuses on more complex organs like the liver and heart [51]. These efforts involve creating vascularized tissues that can integrate seamlessly with the patient's body. Challenges remain, particularly in ensuring these organs function adequately over the long term, but progress is steady, signaling a future where organ shortages could potentially be alleviated through bioprinting technologies [52].

These advancements not only promise to reduce the burden on organ transplant systems but also offer the potential for highly personalized therapeutic options, tailoring treatments to the specific needs and conditions of individual patients. The ongoing convergence of AM technology with cellular and molecular biotechnology continues to push the boundaries of what is possible in tissue engineering and regenerative medicine [53].

1.6 DRUG DELIVERY SYSTEMS

1.6.1 Introduction to Advanced Drug Delivery Systems

Advanced Drug Delivery Systems (ADDS) are engineered technologies designed to transport pharmaceutical compounds to targeted sites within the body in the most efficient way possible [54]. These systems aim to optimize the therapeutic efficacy of medications while minimizing side effects, and enhancing patient adherence to treatment protocols. By achieving controlled release, targeted delivery, and protection of drugs from degradation, ADDS improve patient outcomes significantly [55]. These systems encompass a variety of delivery methods, including nanoparticles, microspheres, transdermal patches, and implantable devices, each tailored for specific types of drugs and therapeutic conditions. The rationale behind ADDS is to circumvent the limitations associated with traditional drug delivery methods, such as nonspecific dispersion, rapid degradation, and fluctuating plasma levels, which can reduce effectiveness and patient compliance [54].

The strategic design of ADDS involves the incorporation of pharmacokinetic properties of drugs, ensuring that they are released at the right time, at the right place, and in the right amount. This precision not only enhances the drug's efficacy but also reduces the potential for toxicity. In chronic disease management, where prolonged drug delivery is needed, ADDS are particularly beneficial, offering sustained therapeutic effects from a single administration. This technology is crucial in treating conditions requiring precise dosages to avoid adverse effects, such as diabetes and hypertension [56].

1.6.2 AM in Drug Delivery

AM plays a transformative role in the field of drug delivery, offering innovative solutions for creating more personalized and effective treatment options. AM

technologies enable the fabrication of complex drug delivery systems that can be tailored to fit the unique needs of individual patients, optimizing the therapeutic outcomes and minimizing side effects [57].

AM techniques allow for the precise configuration of drug dosage forms with controlled geometries that can influence the release and absorption rates of medications. For example, it can produce tablets with specific pore structures or compartments, enabling sequential or delayed release of active ingredients. This capability is particularly advantageous for achieving targeted delivery, multi-drug administration, and customized release profiles, which are difficult to accomplish with conventional manufacturing techniques. This approach is especially beneficial for patients managing multiple conditions, reducing the burden of taking numerous medications daily [58]. AM also supports the development of bioresorbable implants that deliver therapeutic agents directly at the site of disease or injury, enhancing local treatment effectiveness and reducing systemic exposure [59].

Figure 1.4 illustrates the process flow of personalized medicine designing and manufacturing. The process of manufacturing ADDS tablets and pills using AM involves several sophisticated steps, typically using technologies such as FDM, SLS, or Stereolithography (SLA) [60]. Here's how the process unfolds, incorporating exact technologies and ingredient names:

Material Preparation: Pharmaceutical-grade materials used in AM include polymers such as polyvinyl alcohol (PVA), polylactic acid (PLA), or biodegradable medical-grade polymers. These materials are often combined with active pharmaceutical ingredients (APIs) like acetaminophen, ibuprofen, or other drug compounds. The APIs are thoroughly mixed with the polymer base to ensure uniform distribution.

Design and Modeling: Utilizing CAD software, the tablet or pill is designed to specific geometries that dictate the drug release characteristics. This might include multi-layered structures or specific porosity patterns to control the diffusion of the drug.

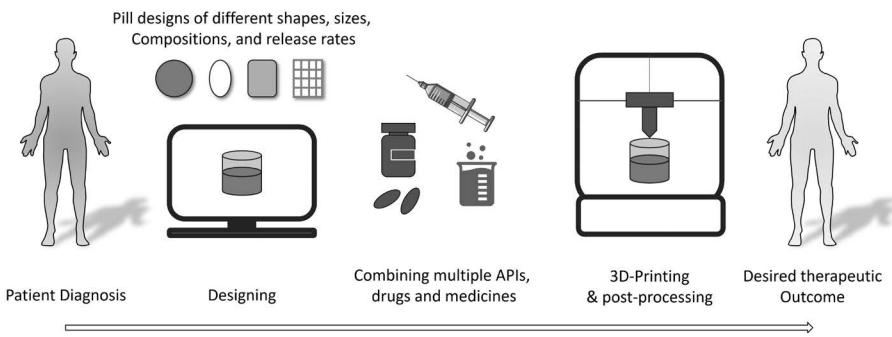

FIGURE 1.4 Typical process flow of personalized medicine designing and manufacturing.

Photograph by the author.

Printing Process:
- *FDM*: It involves the extrusion of a filament of the drug-polymer composite through a heated nozzle, depositing it layer by layer to build the tablet.
- *SLS*: It uses a laser to selectively sinter powdered drug-polymer material, binding them together to form a solid structure.
- *SLA*: It involves a vat of liquid resin that is photo-polymerized layer by layer with a light source, forming the drug-loaded tablet.

Post-Processing: After printing, the tablets undergo various post-processing steps such as drying, curing (in the case of resins), or additional chemical treatments to remove any unreacted materials and ensure that the tablets are safe for patient use.

Quality Control: Rigorous testing is performed to ensure the dosage accuracy, mechanical strength, and release profile of the tablets meet specific medical standards. This includes dissolution testing to observe how the drug releases over time.

Each step is critical to ensure the final product's functionality in terms of targeted drug release profiles and patient-specific dosages. This technology offers the potential for on-demand manufacturing of personalized medications, optimizing therapeutic outcomes for individual patients.

1.6.3 Innovative Applications

The innovative applications of AM in drug delivery are reshaping pharmaceutical care with custom solutions and enhanced drug performance. One of the pioneering applications is the development of 3D-printed "polypills" which incorporate multiple drugs with different release times into a single tablet. This innovation simplifies complex medication schedules for patients with multiple chronic conditions, improving adherence and effectiveness [61]. Another exciting development is the creation of implantable devices tailored to provide controlled, localized drug delivery over extended periods. These implants are particularly useful in treating localized diseases such as certain cancers, where high drug concentrations at the target site can be achieved without systemic toxicity. 3D printing allows these devices to be custom-shaped to fit precise anatomical locations, ensuring comfort and effectiveness [62].

Additionally, AM has facilitated the development of stimuli-responsive drug delivery systems. These smart systems are capable of altering their behavior based on environmental triggers such as pH changes, temperature shifts, or the presence of specific biomarkers. Such responsiveness can significantly improve the efficacy of treatments for diseases like diabetes, where insulin release can be controlled in response to glucose levels [63]. These innovative applications not only demonstrate the potential of AM to revolutionize drug delivery but also highlight its ability to produce more personalized, effective, and safe pharmaceutical therapies. As AM technology continues to evolve, it promises to open new avenues in treatment modalities, further enhancing patient care and outcomes in the healthcare sector [64].

1.7 CHALLENGES, FUTURE TRENDS, AND CONCLUSION

1.7.1 Current Challenges in AM for Biomedical Applications

While AM has significantly advanced biomedical applications, several challenges remain that hinder its widespread adoption. One of the primary concerns is the issue of material biocompatibility. Many materials used in AM need to be rigorously tested to ensure they do not elicit adverse reactions when implanted in the human body. This testing is costly and time-consuming, slowing down the development and approval of new biomedical devices [65].

Another challenge is the reproducibility and quality control of AM processes. Due to the layered nature of 3D printing, variations in print conditions can lead to inconsistencies in the final products, affecting their strength, durability, and performance. This is particularly critical in biomedical applications where device failure can have severe consequences [65]. Establishing standardized protocols and rigorous quality control measures is essential but currently lacks uniformity across the industry.

Regulatory hurdles also pose significant challenges. The regulatory landscape for AM biomedical devices is still evolving, with many countries lacking clear guidelines. This uncertainty can deter innovation and slow down the introduction of new technologies in the healthcare market [66]. Lastly, the high cost of AM technology and the need for specialized knowledge for design and operation are barriers to entry for many healthcare institutions. Although costs are decreasing, the initial investment in AM equipment and training remains substantial, limiting accessibility particularly in less-developed regions [67].

1.7.2 Future Trends in Biomedical AM

The future of biomedical AM is poised for substantial growth, driven by ongoing innovations and increasing adoption across healthcare sectors. One prominent trend is the move toward greater personalization of medical devices and implants. As computational modeling and simulation technologies advance, AM will be able to produce even more complex and tailored devices that perfectly match individual patient anatomy, improving surgical outcomes and patient recovery times [68].

Another emerging trend is the integration of smart technologies into AM devices. With advancements in materials science, future AM-produced devices could include embedded sensors to monitor their function and the healing process in real time [69]. This could lead to a new era of ‘smart implants’ which could provide continuous feedback to both patients and doctors, optimizing treatment plans and predicting potential complications before they become serious.

Bioprinting of tissues and organs is also expected to make significant headway. Researchers are making progress in overcoming current limitations, such as vascularization and cell viability, moving closer to the reality of printing functional organs for transplant, which could dramatically reduce transplant waiting lists and rejection rates [10].

Lastly, sustainability will become a more critical focus. As environmental concerns continue to gain prominence, the development of eco-friendly, biodegradable materials for AM will likely accelerate, reducing the ecological footprint of manufacturing medical devices [68].

1.7.3 Conclusion

AM is revolutionizing the field of biomedicine, offering unprecedented capabilities to customize and innovate across various applications from implants and prosthetics to tissue engineering and drug delivery systems. Despite the challenges posed by material properties, regulatory environments, and cost, the potential benefits of AM in improving patient outcomes and operational efficiencies are substantial.

As the technology continues to mature and overcome existing obstacles, its integration into mainstream medical practices seems inevitable. The future of AM in biomedicine is not just about enhancing current practices but transforming them. It promises a shift toward more personalized, responsive, and sustainable medical treatments that could redefine what is possible in healthcare and medicine. By continuing to foster interdisciplinary collaboration and investing in research and development, the biomedical sector can harness the full potential of AM to better meet the needs of patients and providers alike.

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2 Pre- and Post-Processing Techniques in Additive Manufacturing for Orthopedic Implants

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2.1 INTRODUCTION

In recent years, additive manufacturing (AM), also referred to as 3D printing, has become a revolutionary technology in the manufacturing of orthopedic implants. Its ability to offer patient-specific customization and reduce adaptation time within the human body has led to its widespread adoption in biomedical applications. However, despite these advantages, poor surface quality remains a significant challenge in 3D-printed implants [1, 2]. Surface imperfections, such as partially melted powder particles and pores, negatively affect the functionality of implants, necessitating comprehensive post-processing techniques to enhance surface finish and reduce roughness [3, 4]. Stainless steel (SS316L), Cobalt (Co)-based alloys, titanium (Ti)-based alloys are the most widely used biomaterials in orthopedic implants due to their high toughness, cost-efficiency, and biocompatibility [5–7]. However, its relatively low hardness compared to other biomaterials results in increased wear, which poses a long-term risk for patients. The wear rate, compounded by surface quality issues in additively manufactured parts, generates small debris particles that can lead to complications such as aseptic loosening and inflammatory responses [8, 9]. Moreover, Researchers are also exploring high entropy alloys such as Ti-Ta-Nb-Mo-Zr, Ti-Zr-Hf-Nb, Ti-Ta-Hf-Nb-Zr, and Ti-Ta-Zr-Nb, as biomaterials for the orthopedic implant applications [10–12].

This chapter delves into the pre and post-processing techniques that are critical in the AM of orthopedic implants. In the pre-processing stage, the design and optimization of implants using computer-aided design (CAD) and finite element analysis (FEA) ensure mechanical strength and durability while minimizing material usage. Additionally, the selection of biocompatible materials, including Ti-based alloys and Co-based alloys, is crucial to prevent adverse reactions in the human body. On the post-processing side, surface finishing operations such as laser polishing, electro-polishing, and abrasive flow finishing (AFF) are explored to enhance the mechanical properties and biocompatibility of implants. These techniques are vital for reducing wear rates and improving the osseointegration of implants,

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thereby facilitating better integration with bone tissue. Ultimately, the success of 3D-printed orthopedic implants depends on a well-coordinated workflow, from pre-processing design and material selection to post-processing surface finishing and quality control. As this chapter will illustrate, advancements in pre and post-processing techniques not only improve the functionality and safety of implants but also push the boundaries of medical innovation, leading to more effective, patient-specific solutions in orthopedic care.

2.2 PRE-PROCESSING TECHNIQUES

Pre-processing is a critical stage in the manufacturing of orthopedic implants, where various techniques ensure that the final product meets the stringent requirements of biocompatibility, mechanical strength, and functional suitability. In this chapter, we will discuss several key pre-processing techniques, including material selection, design using CAD, slicing, support structure generation, and pre-print inspection, all essential in ensuring the creation of high-quality, reliable implants. These techniques are critical in both traditional manufacturing and the emerging field of AM, which holds promise for more personalized and efficient implant production.

2.2.1 Material Selection for Orthopedic Implants

One of the most crucial steps in pre-processing is selecting the appropriate material for an orthopedic implant. The material must meet specific biocompatibility, mechanical, and functional requirements to ensure the implant functions correctly within the human body [13]. Table 2.1 presents the required properties for knee

TABLE 2.1
Required Properties for Knee Implant Material and Consequences of Not Having It [1, 5, 11]

Required Property for Knee Implant Material	Consequences of Not Having the Required Property
Biocompatibility	Response of human body; Adverse effects on the immune system
Osseointegration	Inadequate integration between knee implant and human tissues and bones
Higher corrosion resistance	Releasing non-compatible metallic ions to human blood Allergic reactions
Modulus of elasticity closer to human bones	Stress shielding effect due to loosening of implant components Severe inflammatory response Destruction of healthy bones
Adequate yield and compressive strength	Implant failure, pain to patient, and revision surgery
Higher wear resistance	Mixing of wear debris in human blood leads to carcinogenicity
Longer fatigue life	Mechanical failure of knee implant, Need of revision surgery

implant material that will help longer life of knee implants in the human body and they are described in the following paragraphs:

It can be seen from Table 2.1 that the most priority is given to biocompatibility, which is paramount in orthopedic implants. The material must not induce an immune response or toxicity when in contact with body tissues and fluids. Historically, metals like stainless steel, cobalt-chromium alloys, and titanium have been widely used due to their durability and compatibility [14].

Titanium and its alloys, for instance, are not only corrosion-resistant but also encourage osseointegration, the process where bone grows into the implant, forming a stable bond [15]. Ceramics, including alumina and zirconia, are also common due to their wear resistance and inertness. For example, alumina ceramics offer low friction, making them ideal for joint implants. Polymers such as ultra-high-molecular-weight polyethylene (UHMWPE) are used in load-bearing areas due to their excellent wear resistance and low friction [16]. Recent developments include bioresorbable materials, which can degrade safely within the body. These materials, often composed of polymers like polylactic acid (PLA), are ideal for temporary implants used in healing fractures [17].

In addition to biocompatibility, the mechanical properties of the selected material must be suitable for the stresses the implant will face. For example, hip and knee implants must endure constant loading and stress, requiring materials with high tensile strength, fatigue resistance, and stiffness. Stainless steel and cobalt-chromium alloys are chosen for such applications due to their superior mechanical properties [18]. Elastic modulus is another essential consideration. A mismatch between the modulus of the implant and the surrounding bone can lead to stress shielding, where the bone deteriorates due to the uneven distribution of mechanical forces [19]. Therefore, materials with a modulus close to that of human bone, such as titanium alloys, are often preferred. The suitability of materials varies depending on the implant's intended function and location within the body. For load-bearing implants like hip and knee joints, metals and ceramics that offer high strength and wear resistance are favored. For spinal implants, biocompatible metals like titanium alloys are ideal due to their ability to promote osseointegration while offering the required strength. In contrast, for non-load-bearing applications such as cranial implants, polymers may be more appropriate because they are lightweight, radiolucent, and can be designed to degrade over time as natural bone regenerates. Each selection of materials process is a balancing act between biocompatibility, mechanical requirements, and patient-specific needs.

2.2.2 Computer-Aided Design (CAD) for Implant Customization

CAD design has revolutionized the way implants are designed, allowing for more precise and customized solutions tailored to individual patient anatomy. This customization is crucial for improving implant fit and function, thereby enhancing patient outcomes. CAD provides several advantages in orthopedic implant design. First, it allows for the precise modeling of complex geometries, which is especially useful in creating custom implants that conform to the specific anatomy of a patient. The software also enables designers to simulate the mechanical behavior of implants under various physiological conditions, allowing for the optimization of material

use and structural integrity before manufacturing. Additionally, CAD models can be easily shared and modified by a team of engineers, surgeons, and other stakeholders, improving communication and collaboration. The use of CAD also integrates well with AM techniques, where digital designs are directly translated into physical objects, enabling faster prototyping and production. One of the significant benefits of CAD is the ability to create personalized implants tailored to the individual patient. Each person's anatomy is unique, and using patient-specific data obtained from imaging techniques like computed tomography (CT) scans or MRIs, engineers can design implants that offer a perfect fit. This results in improved surgical outcomes, shorter recovery times, and a reduced risk of complications such as implant failure or tissue damage [20]. Personalized implants are particularly beneficial in cases where standard implants may not fit properly due to deformities or complex bone structures. The use of CAD in these situations allows for the creation of bespoke implants that precisely mimic the anatomy of the patient, enhancing comfort and functionality.

Once the implant design is finalized, the next step in AM is slicing and the generation of support structures. These processes are crucial in ensuring the successful printing of complex implant geometries. Slicing refers to the process of dividing the CAD model into thin layers, which are then printed sequentially in the AM process. The choice of layer thickness has a significant impact on the final product. Thinner layers generally result in a smoother surface finish and higher resolution but take longer to print, while thicker layers can reduce print time but may sacrifice detail. Slicing software also allows for the optimization of printing parameters, such as infill density, speed, and support generation. Correctly slicing the model is essential for achieving the desired mechanical properties, surface finish, and accuracy. Support structures play a vital role in AM, particularly in complex geometries and overhangs. These structures provide the necessary stability during the printing process, preventing warping, collapsing, or other defects [21]. They also help maintain the dimensional accuracy of the implant, ensuring that the final product matches the original CAD design. In metal AM, support structures are often required to conduct heat away from the build, reducing thermal stresses that could lead to cracking or deformation. However, the design of support structures must be carefully considered to ensure that they are easily removable without damaging the finished implant.

2.2.3 Pre-Print Inspection and Validation

Before the printing process begins, rigorous inspection and validation are essential to ensure that the design meets all required specifications and that the printing process will proceed smoothly. Quality control in the pre-processing phase includes the verification of the CAD model, the accuracy of the slicing parameters, and the appropriateness of the material selection. Advanced simulation tools can be used to predict how the material will behave during and after printing, allowing for the identification of potential issues before manufacturing begins. Moreover, pre-print inspections often involve ensuring that the selected material batch meets all biocompatibility and mechanical property standards, further reducing the risk of implant failure post-manufacture. Pre-print validation includes identifying and rectifying potential flaws that could compromise the final product. These flaws might include

inadequate support structures, incorrect layer thickness, or improper orientation of the model. Engineers and technicians work closely to ensure that all aspects of the design and slicing process are optimized for the highest-quality output. By addressing these potential issues before printing begins, manufacturers can avoid costly post-processing steps, reprints, or even failures in the field. This step is vital in ensuring that the orthopedic implant will function as intended, providing patients with reliable, long-lasting solutions to their medical needs.

2.3 ADDITIVE MANUFACTURING TECHNIQUES FOR ORTHOPEDIC IMPLANTS

AM has revolutionized the field of orthopedic implants. Traditionally, orthopedic implants such as joint replacements, spinal implants, and other prostheses were manufactured using subtractive processes like machining and casting. While these methods offer a high degree of precision, they are often limited in terms of design flexibility, material use, and customization [22]. AM has addressed many of these limitations by allowing for the creation of complex geometries, the integration of patient-specific designs, and the use of advanced biomaterials [23]. This section explores the various AM techniques used for orthopedic implants, with a detailed focus on Powder Bed Fusion (PBF) techniques such as Selective Laser Melting (SLM) [24] and Electron Beam Melting (EBM) [25], Directed Energy Deposition (DED) [26], Binder Jetting [27], Material Extrusion [28], and Vat Photopolymerization [29].

2.3.1 Powder Bed Fusion Techniques

PBF techniques are among the most widely used AM methods for producing orthopedic implants. These processes involve the use of a laser or electron beam to selectively fuse powdered materials layer by layer, based on a digital model of the implant. The major advantage of PBF techniques is their ability to produce highly detailed and complex geometries that would be difficult or impossible to create using traditional manufacturing techniques. Additionally, PBF allows for the use of various biocompatible materials, including titanium alloys, cobalt-chromium alloys, and polymers, which are commonly used in orthopedic applications due to their strength, corrosion resistance, and biocompatibility.

2.3.1.1 Selective Laser Melting (SLM)

SLM is a type of PBF technique that uses a high-power laser to melt and fuse metal powders, layer by layer, to form a solid part. SLM is particularly well-suited for producing orthopedic implants because it allows for the creation of parts with intricate geometries, including lattice structures that mimic the porous nature of bone. These lattice structures are essential for enhancing osseointegration, where the implant bonds with the surrounding bone tissue, providing long-term stability and reducing the risk of implant failure. SLM is commonly used to produce titanium alloy (Ti-6Al-4V) implants, which are widely regarded as the gold standard for orthopedic applications due to their high strength-to-weight ratio and excellent biocompatibility. Titanium alloys produced using SLM have shown comparable or

even superior mechanical properties to those produced using traditional manufacturing methods. Furthermore, the design flexibility of SLM allows for the production of patient-specific implants, which can be tailored to the unique anatomy of the patient, improving the overall fit and function of the implant. Research has demonstrated that SLM-produced implants with porous structures can significantly improve osseointegration compared to traditional solid implants. The porosity of these implants can be controlled during the manufacturing process, allowing for the optimization of mechanical properties such as stiffness and strength, which are critical for matching the mechanical behavior of the implant to that of natural bone. Additionally, the ability to incorporate antimicrobial coatings or drug-delivery systems into the SLM process holds promise for reducing the risk of infection following implantation.

2.3.1.2 Electron Beam Melting (EBM)

EBM is another type of PBF technique, but instead of using a laser, EBM utilizes a high-energy electron beam to melt metal powders. EBM is particularly suitable for orthopedic implants because it can produce parts with high density and excellent mechanical properties. Like SLM, EBM allows for the production of complex geometries, including porous structures that enhance osseointegration. One of the key advantages of EBM over SLM is its ability to process reactive materials like titanium in a vacuum environment, which reduces the risk of oxidation and contamination. This is especially important for orthopedic implants, as the long-term performance of the implant is heavily influenced by its surface properties and material integrity. EBM is also known for its ability to produce parts at a faster rate than SLM, making it a more efficient option for mass production of implants. EBM has been used to produce a wide range of orthopedic implants, including acetabular cups for hip replacements, spinal cages, and knee components. The implants produced using EBM have demonstrated excellent mechanical properties, such as high fatigue strength and corrosion resistance, making them suitable for long-term use in the human body. Additionally, the ability to create porous structures with controlled pore size and distribution has been shown to enhance the biological response of the surrounding bone tissue, leading to improved implant stability and longevity.

2.3.2 Directed Energy Deposition (DED)

DED is another AM technique used for orthopedic implants. Unlike PBF, which builds parts layer by layer from a powder bed, DED uses a focused energy source, such as a laser or electron beam, to melt and deposit material onto a substrate. The material is typically fed in the form of powder or wire, and the energy source melts the material as it is deposited, creating the part layer by layer. DED offers several advantages for orthopedic implants, including the ability to repair or modify existing implants and the ability to build large, complex parts with high precision. DED is particularly useful for producing hybrid implants that combine different materials or for creating functionally graded materials, where the material composition changes gradually throughout the part. This can be beneficial for implants that

require different mechanical properties in different regions, such as a combination of strength and flexibility. One of the key applications of DED in orthopedics is the repair of damaged or worn implants. For example, if an implant has been in use for several years and has developed wear or damage, DED can be used to add material to the damaged area and restore the implant to its original condition. This reduces the need for complete implant replacement and can extend the life of the implant, reduce costs and improving patient outcomes. Additionally, DED can be used to produce custom implants with patient-specific geometries. By using medical imaging data, such as CT or MRI scans, the exact shape and size of the implant can be tailored to the patient's anatomy, resulting in a better fit and improved performance. This level of customization is particularly important for complex joint replacements, where the shape of the implant must match the contours of the patient's bones to ensure proper alignment and function.

2.3.3 Binder Jetting

Binder Jetting is an AM process that uses a liquid binder to selectively bond layers of powdered material. Unlike PBF and DED, which use heat to fuse materials, Binder Jetting relies on the binder to hold the particles together until the part is fully built. After the part is printed, it is typically subjected to a post-processing step, such as sintering, to improve its mechanical properties. Binder Jetting is particularly useful for producing orthopedic implants with complex geometries and fine details. The process is relatively fast and can produce parts with high resolution and accuracy. Additionally, Binder Jetting allows for the use of a wide range of materials, including metals, ceramics, and polymers, making it a versatile option for producing different types of implants. One of the main advantages of Binder Jetting for orthopedic implants is its ability to produce parts with controlled porosity. By adjusting the binder and powder composition, the porosity of the implant can be tailored to promote osseointegration and reduce the risk of stress shielding, where the implant takes on too much load, causing the surrounding bone to weaken. Furthermore, Binder Jetting allows for the production of multi-material parts, where different materials are used in different regions of the implant to optimize performance.

2.3.4 Material Extrusion

Material Extrusion, specifically Fused Deposition Modeling (FDM), is an AM process that uses a heated nozzle to extrude thermoplastic material layer by layer to build a part. While FDM is commonly associated with polymer-based parts, recent advancements have enabled the use of FDM for producing metal and composite implants. FDM is particularly advantageous for producing low-cost, patient-specific implants, especially for prototyping and pre-surgical planning. By using biocompatible polymers, such as polyether ether ketone (PEEK), FDM can produce temporary or permanent implants with properties tailored to the specific needs of the patient. The ability to customize implant designs based on patient-specific data, such as MRI or CT scans, has made FDM a popular choice for custom orthopedic implants.

2.3.5 Vat Photopolymerization

Vat Photopolymerization is an AM process that uses light to cure liquid resin into solid parts. Stereolithography (SLA) and Digital Light Processing (DLP) are two common forms of this technique. SLA uses a laser to cure the resin, while DLP uses a digital projector to cure entire layers at once. SLA and DLP are widely used for producing highly detailed and precise parts, making them ideal for producing small orthopedic implants and surgical guides. The ability to produce parts with complex geometries and smooth surfaces makes these techniques suitable for applications where high precision is required. Additionally, SLA and DLP allow for the use of biocompatible resins, which can be used for temporary implants or pre-surgical models. The high resolution and accuracy of these processes make them invaluable tools in the development of custom, patient-specific orthopedic solutions.

2.4 POST-PROCESSING TECHNIQUES

In the world of AM techniques, the production of complex geometries and functional parts, such as implants, has seen tremendous advancements. However, the printed parts are rarely ready for direct application without going through rigorous post-processing techniques. The mechanical, biological, and aesthetic performance of orthopedic implants depends heavily on various post-processing steps to enhance their functionality, durability, and biocompatibility [30]. These post-processing methods include cleaning and removal of excess powder, stress relief heat treatment, surface finishing, and post-print inspection and quality control. Post-processing serves as the critical bridge between the AM process and the final usability of the implants. It helps meet specific functional and regulatory requirements, ensuring implants are safe, reliable, and fit for long-term use in medical applications. In this chapter, we will discuss the various post-processing techniques employed to enhance the performance and quality of additively manufactured implants.

2.4.1 Cleaning and Removal of Excess Powder

Cleaning and removing excess material or feedstock powder is the first and most crucial step in post-processing, especially for AM processes like Laser Powder Bed Fusion (LPBF), Selective Laser Sintering (SLS), and EBM. During the printing process, not all the powder material is fused, leaving a considerable amount of loose or semi-fused material adhering to the manufactured part. For implants to meet clinical standards, this powder must be thoroughly cleaned and removed. Cleaning plays a pivotal role in preparing an implant for subsequent post-processing steps, such as surface finishing and coating applications. Proper cleaning is crucial not only for the aesthetic appeal of implants but also for their mechanical performance and biocompatibility. The powder or debris left over on the implant surface can lead to surface defects that compromise the overall structural integrity of it. In medical applications, any residual particles can trigger inflammatory reactions, making it critical to ensure that the surface is entirely clean and free of contaminants. Furthermore, improper cleaning can lead to complications in subsequent steps such as surface polishing, where leftover powder can interfere with achieving the desired surface smoothness

and could even scratch or deform the surface of the part. The quality of cleaning directly influences the implant's biocompatibility, making it vital for patient safety.

Complex geometries of orthopedic implants pose significant challenges during cleaning. Implants often have intricate lattice structures, internal channels, and undercuts that are difficult to reach, making powder removal particularly challenging. Incomplete removal of excess powder in these geometries can lead to mechanical failure or biocompatibility issues. Various techniques are used to overcome these challenges, including ultrasonic cleaning, air-blasting, and vacuum suction. Ultrasonic cleaning is particularly effective for complex structures, as it uses high-frequency sound waves in a liquid medium to agitate and dislodge trapped powder particles. Air-blasting techniques involve using high-pressure air jets to clean the implant's surface and internal cavities. More advanced methods include automated powder removal systems that employ robotic arms and specialized nozzles to target hard-to-reach areas. In cases where powder removal is exceptionally difficult, using soluble support structures during the printing process can be a helpful solution. These supports are made from materials that dissolve easily in a post-print cleaning bath, leaving the desired geometry free of debris.

2.4.2 Stress Relief Heat Treatment

AM processes often introduce significant residual stresses in printed parts due to the rapid heating and cooling cycles involved. These residual stresses, if not addressed, can lead to mechanical failures such as cracking, warping, and distortion. Stress relief heat treatment is a crucial post-processing step aimed at reducing these stresses and improving the mechanical properties of the implant. Residual stresses arise in AM implants as a result of thermal gradients created during the layer-by-layer printing process. Different areas of the part experience varying degrees of heating and cooling, causing internal stresses that are locked into the material. These stresses can lead to premature failure under mechanical loads or degrade the implant's overall performance in the body. Stress relief heat treatment typically involves heating the implant to a specific temperature and holding it at that temperature for a set duration before cooling it down in a controlled manner. The temperature and duration depend on the material being used, with common materials like titanium and cobalt-chrome alloys requiring tailored heat treatment cycles. By undergoing stress relief, the implant's material structure is homogenized, allowing the redistribution of internal stresses and reducing the likelihood of failure during use.

In addition to relieving residual stresses, heat treatment can significantly enhance the mechanical properties of the implant, such as strength, hardness, and fatigue resistance. For metallic implants, heat treatment promotes the diffusion of atoms within the material, creating a more uniform grain structure. This grain refinement results in increased tensile strength and fracture toughness, which are critical for implants subjected to cyclic loading in the human body, such as hip or knee replacements. For implants made from titanium alloys, specific heat treatments like aging can be used to precipitate secondary phases that improve the hardness and wear resistance of the material. Such treatments are particularly important in load-bearing orthopedic implants that must endure long-term mechanical stress without wearing down prematurely.

2.4.3 Surface Finishing

Surface finishing is one of the most important post-processing steps, especially for orthopedic implants that require high levels of biocompatibility and aesthetic quality. It involves a series of polishing and coating techniques to smoothen the surface and improve the implant's interaction with biological tissues.

2.4.3.1 Polishing Techniques for Improved Biocompatibility

Polishing is crucial for enhancing the biocompatibility of implants. Rough or irregular surfaces can provoke unwanted immune responses when implanted in the body. For orthopedic implants, a smooth surface reduces friction with surrounding tissues, minimizing the risk of inflammation, infection, or implant rejection. Common polishing techniques include mechanical polishing, electrochemical polishing (or electropolishing), and chemical etching. Mechanical polishing employs abrasive materials for physical smoothing, while electrochemical polishing uses an electric current to dissolve microscopic layers, resulting in a mirror-like finish. Chemical etching can also eliminate surface imperfections.

During the SLM process, partially molten metal powders can adhere to the surface of the part. Sandblasting can be used to remove these adhered unwanted powder particles, thereby improving the surface quality. However, this process can also cause local plastic deformation on the surface of the affected portion of the part which may alter the surface roughness. It is influenced by the process parameters like pressure and blasting duration. Higher pressure and longer durations typically make the part surface rougher. The opinion of the expert is required in the selection of the sandblasting particles and their material. Selection of the particle size is very important because a bigger particle size may excessively remove material from the part surface. Whereas metal-type particles can create a more abrasive effect, while glass-type particles can shatter, leaving sharp edges that may damage the surface. Teo et al. [31] demonstrated that sandblasting significantly reduced the surface roughness of additively manufactured lattices using glass particles at specific pressures and distances. Similarly, Navickaitė et al. [32] achieved a substantial reduction in surface roughness of titanium alloys using plasma electrolyte polishing, while Yamaguchi and Graziano [33] reported over a 50% reduction in surface roughness for cobalt-chromium alloys through magnetic abrasive finishing.

In another study, Kaynak and Kitay [34] investigated various finishing processes, including machining, vibratory surface finishing (VSF), and drag finishing (DF), for SLM-manufactured 316L stainless steel. The initial average surface roughness of approximately 7 μm was reduced to 2.7 μm after 4 hours of DF, while the VSF process produced a surface roughness of 4.1 μm.

2.4.3.2 Laser-Based Processes

The development of laser-based surface treatments has primarily focused on enhancing the surface morphology of AM metallic parts. These treatments are typically applied post-AM fabrication to reduce surface irregularities. One such method, laser shot peening (LSP), is widely used across various industries for components like fan blades, turbine blades, and gears. During the peening process, the material

undergoes plastic compression in the normal direction, causing lateral expansion, which in turn induces beneficial compressive residual stresses. This process is particularly effective for extending the fatigue life of implants by introducing compressive residual stress on the surface [35]. Their study found that LSP treatment of Ti-6Al-4V alloy can enhance the longevity of medical implants, potentially lowering the cost and recovery time by reducing the need for re-surgery. A key parameter in LSP is laser power density, and the procedure can be performed with or without a protective coating on the workpiece surface.

Zhang et al. [36] demonstrated that LSP increased the hardness and yield strength of AZ31B Mg alloy. This hardening significantly improved the wear resistance and fatigue performance of the alloy. Immersion tests in a cell culture medium revealed that LSP did not noticeably increase Mg^{2+} release or weight loss. Additionally, in vitro cell culture tests showed that LSP-treated samples exhibited cell compatibility similar to untreated samples, supporting the potential clinical use of Mg alloys in orthopedics. Vishnu et al. [37] examined the effect of varying laser power per unit area on surface topography, fretting wear, biocompatibility, oxide composition, and wettability of low-modulus Ti-22Nb and Ti-35.4Nb alloys. They found that higher laser fluence improved hydrophilic behavior and formed oxide layers rich in Ti^{4+} and Nb^{5+}. The presence of Nb^{5+} rendered the oxide surfaces less defective, enhancing fretting wear resistance. They concluded that surfaces treated with laser power densities of 6 and 9 GW/cm^2 on Ti-22Nb alloy could significantly improve both fretting wear resistance and biocompatibility.

Guo et al. [38] applied LSP to Ti-6Al-4V alloy manufactured using laser AM. Their study investigated microstructural evolution, microhardness distribution, residual stress, and mechanical properties. LSP led to grain refinement, with the average grain size of the α phase decreasing from 33.6 to 24.3 μm. Residual stress shifted from tensile to compressive, affecting a depth of around 700 μm, while the hardening layer extended to about 900 μm. Grain refinement contributed to improvements in yield strength, ultimate tensile strength, and elongation. Okura et al. [39] explored cavitation peening, shot peening, and laser peening to improve the fatigue life of Ti-6Al-4V alloy manufactured by EBM. Through plane bending fatigue tests, they measured residual stress, yield stress, hardness, and established correlations between mechanical properties and fatigue life. Similarly, Tian et al. [40] employed laser polishing to reduce surface roughness to less than 0.51 μm in Ti-6Al-4V parts produced using EBM. Yasa et al. [41] utilized laser re-melting during SLM of 316L stainless steel and Ti-6Al-4V parts to enhance surface quality. Re-melting the same layer using a continuous wave laser improved density, surface quality, and microhardness in the final product.

2.4.3.3 Abrasive Flow Finishing Process

AFF processes utilize viscoelastic putty containing abrasive particles that can flow over surfaces and inside intricate geometries to reduce surface roughness. There are two main types of AFF processes: (i) one-way AFF and (ii) two-way AFF (Figure 2.1). This method only requires a specialized fixture tailored to the geometry of the workpiece so that the semi-solid deformable putty can flow across the target surfaces [42]. While there is extensive research on finishing biomedical implants using AFF, the focus on finishing additively manufactured biomedical implants using AFF is discussed below.

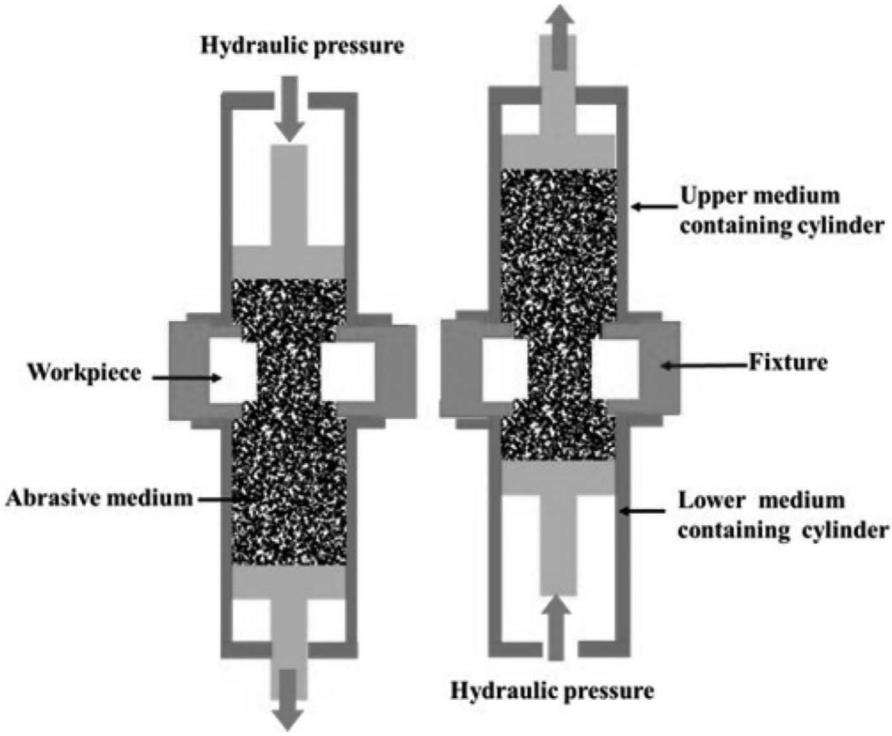

FIGURE 2.1 Schematic of the two-way abrasive flow finishing (AFF) process and its working.

Source: Rana et al. [42]. Reprinted with permission from Springer @ 2020.

AFF is a non-conventional finishing technique that provides high accuracy, efficiency, consistency, and cost-effectiveness in finishing complex and hard-to-machine materials/components. It also offers the potential for automation, making it valuable to the manufacturing sector. Meena et al. [43] applied the AFF process to post-process the femoral head of a hip joint manufactured using SLS. Hashmi et al. [44] employed AFF to finish the surface of a femoral component for a knee implant replica used in investment casting applications. For a femoral component printed with FDM, a corn-starch-based medium (50% corn-starch powder) achieved an 83% improvement in surface roughness (Ra), reducing the initial surface roughness by 81.58%, from 9.30 to 2.10 µm. In another study, Hashmi et al. [45] developed eco-friendly abrasive media to finish 3D-printed biomedical PLA parts. They also created artificial neural network (ANN) models to optimize the process parameters for both AFF and FDM processes.

2.4.3.4 Electrochemical Finishing Process

Electrochemical finishing (ECF) operates based on Faraday's law of electrolysis, where the material is removed atom by atom from the anode surface i.e., the workpiece. Figure 2.2 depicts the working of the ECF process. In this process, the tool

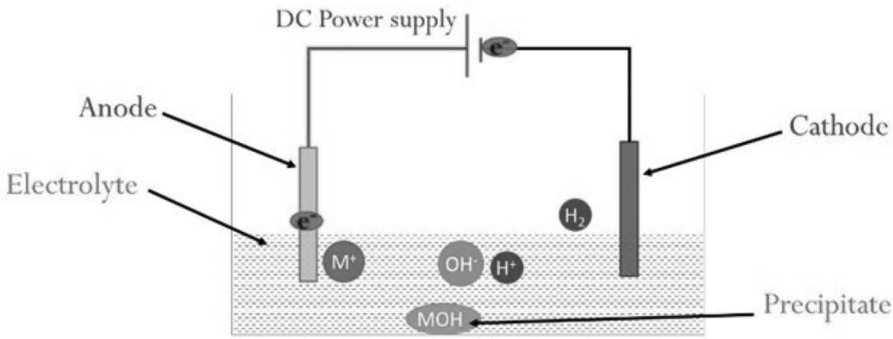

FIGURE 2.2 Working on electrochemical finishing.

serves as the cathode and is connected to the negative power supply, while the workpiece is the anode, connected to the positive power supply. A small voltage is applied between the anode and cathode, and several process parameters influence the outcome, including applied voltage, cathode material, interelectrode gap (IEG), electrolyte type and concentration, electrolyte flow rate, and temperature. Optimizing these parameters is key to achieving better-finishing results.

In the context of orthopedic implants, Bagehorn et al. [46] used electropolishing to significantly reduce the initial surface roughness, with an average Ra of 16.6 ± 1.0 µm, down to a final Ra of 2.7 µm ± 0.4 µm within 60 minutes. Luo et al. [47] investigated the effects of ECF on the biocompatibility of additively manufactured lattice-structured β-type Ti-Ni-Ta-Zr alloys. They found that using an electrolyte mixture of 30% oxalic acid and 70% acetic acid effectively dissolved balling defects and formed an approximately 21 nm amorphous clad layer on the material surface after finishing. This clad layer acted as a barrier, preventing Ta and Zr ions from leaching into muscle tissue and promoting tissue regeneration at the implantation site over a four-week period. Additionally, cell cytotoxicity decreased, and blood biocompatibility improved after finishing, with cells on the electropolished Ti-Ni-Ta-Zr showing higher antioxidant capacity but lower proliferation compared to the as-printed material.

2.4.3.5 Electrical Discharge Finishing

Additive mixed-electric discharge machining (AM-EDM) is an emerging technology that serves both as a machining and surface modification technique. Beyond its traditional use for molds, dies, and tool fabrication, AM-EDM is being increasingly applied to finish components for the automotive, aerospace, nuclear, and biomedical industries through material migration. The mechanism of material transfer in AM-EDM is similar to electrophoretic deposition, where additives in the dielectric fluids melt and migrate to the machined surface, forming a mirror-like finish with extremely hard, nanostructured, and nanoporous layers. These layers promote bone ingrowth and improve cell adhesion. Implant shaping and surface treatment using AM-EDM have gained significant research attention in recent years. Jithinraj et al. [48] and Aliyu et al. [49] employed wire electrical discharge polishing to finish metallic components produced using the LPBF process. Their research focused on the surface

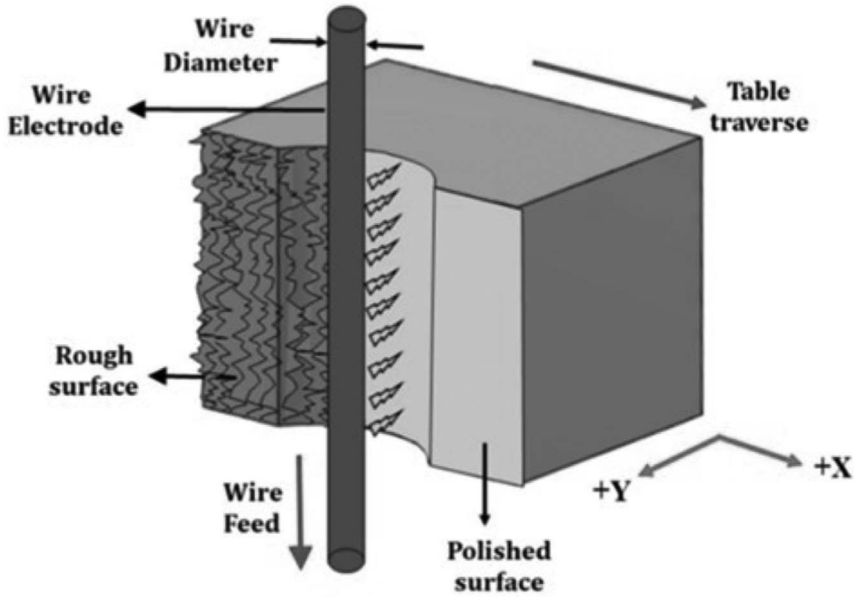

FIGURE 2.3 Schematic of wire electrical discharge finishing process.

Source: Jithinraj et al. [48]. Reprinted with permission from Elsevier @ 2022.

quality and form accuracy of curved and inclined AlSi10Mg workpieces. They observed a 68% reduction in cylindricity error, a 75% reduction in flatness error, and a 50–60% reduction in surface roughness. In some cases, EDM was also used to increase surface roughness, enhancing the exposed surface area. Figure 2.3 shows the schematic of the wire electrical discharge finishing (WEDF) process. Singh et al. [50] investigated the effect of WEDF on the bio-functionalities of Ti-6Al-7Nb alloy, focusing on apatite formation, metal ion release rate, and antibacterial activities. After surface modification, they found an increase in apatite formation, a reduction in the metal ion release rate, and enhanced antibacterial bioactivity on the Ti-6Al-7Nb alloy.

2.4.3.6 Magnetorheological Fluid Assisted Finishing

The Magnetorheological Fluid Assisted Finishing (MFAF) process is an advanced surface finishing technique that leverages the unique properties of magnetorheological (MR) fluid to improve the surface quality of a workpiece without altering its surface topography. In this process, the MR fluid, influenced by a magnetic field, acts as a polishing tool to enhance the surface finish. The MR fluid consists of ferromagnetic particles combined with abrasive particles, suspended in a carrier medium, and stabilized to prevent the sedimentation of heavier particles. The interaction between the workpiece and MR fluid creates abrasion on the surface, reducing surface roughness and achieving a uniform finish. Average surface roughness (Ra) provides information on the mean depth of valleys and height of peaks from the central line, though it offers limited insight into the characteristics of the produced peaks and valleys.

Karthikeyan et al. [51] used rotational magnetorheological AFF to finish the surface of SS 316L and studied the surface wettability, bio-corrosion, and hemocompatibility. They found that implant surface change from hydrophobic to hydrophilic, corrosion resistance, and hemocompatibility were improved. Rajput et al. [3] used SLM to manufacture the biomaterial using SS316L powder. They found that the initial average surface roughness of 8.32 was reduced to 32.46 nm which is a very highly finished surface. They also performed a wear test using the pin-on-disc method and found that the wear resistance of the polished surface was improved.

Rajput et al. [52] used SLM to manufacture the femoral head of Ti-6Al-4V and finished it by chemical etching and hybrid electrochemical-magnetorheological (H-ECMR) finishing. They found that the additively manufactured surface was hydrophilic after the finishing with H-ECMR and this process produced a thick oxide layer on the surface which helps in improving the corrosion resistance of the implant. They also found that LPBF-manufactured Ti-6Al-4V femoral have more wear resistance after finishing with H-ECMR

2.4.3.7 Coatings and Their Role in Orthopedic Implants

Surface coatings are crucial in improving the biological performance of implants. They can enhance wear resistance, promote osseointegration (the direct bonding between implant and bone), and reduce friction. Common coatings for orthopedic implants include hydroxyapatite (HA), titanium nitride (TiN), and diamond-like carbon (DLC). Hydroxyapatite is widely used for its biocompatibility and ability to encourage bone ingrowth, facilitating better integration between the implant and surrounding bone, leading to faster healing and more stable fixation. Titanium nitride offers a hard, wear-resistant surface, reducing friction in joint replacements, while DLC coatings provide low friction and high hardness, making them ideal for implants subjected to high wear.

To prevent corrosion in magnesium (Mg) alloys and preserve long-term mechanical support, surface treatments have proven effective [53]. Such treatments enhance both cell compatibility and mechanical stability by modifying surface properties [54]. Several surface treatment methods for Mg alloys are available, as illustrated in Kaushik V [55]. Lindahl et al. [56] successfully coated additively manufactured CoCr substrates by immersing them in phosphate-buffered solutions with Ca^{2+}, demonstrating the feasibility of coating intricate parts. Vladescu et al. [57] studied how pH modification affects the corrosion behavior, morphology, and biocompatibility (both in vitro and in vivo) of electrochemically assisted deposition of hydroxyapatite on additively manufactured Ti64 samples. Hu et al. [58] applied a bioactive ceramic coating using femtosecond laser (FS) and micro-arc oxidation (MAO) treatments. The FS treatment improved surface finish, optimizing MAO coatings on additively manufactured titanium alloys, leading to enhanced corrosion resistance, adhesive strength, and biological performance compared to conventional sandblasting and acid-etching techniques. Rifai et al. [59] utilized polycrystalline diamond coatings on additively manufactured titanium, enhancing scaffold interaction for medical implants. They observed increased mammalian cell growth, enhanced apatite deposition, and reduced microbial activity. Karaji et al. [60] applied electrophoretic deposition of a silk fibroin solution containing tricalcium phosphate (TCP) and

vancomycin on porous titanium, which exhibited antibacterial properties. Assays revealed significant increases in cell density and calcium deposition in the coated groups, highlighting osteogenic differentiation. Guo et al. [61] applied a graphene oxide (GO) coating with nano-hydroxyapatite (HA) to NiTi alloys using DC electrodeposition, showing improved corrosion resistance and biocompatibility.

2.4.4 Post-Print Inspection and Quality Control

The final step in the post-processing workflow involves rigorous inspection and quality control measures to ensure the implant meets stringent regulatory and performance standards. The ability to guarantee the dimensional accuracy and structural integrity of an implant is essential for its successful clinical application. Non-destructive testing (NDT) techniques allow for the inspection of the implant's internal and external structures without causing damage. Common NDT methods used in the post-processing of implants include X-ray CT, ultrasonic testing, and dye penetrant inspection. X-ray CT is particularly useful for inspecting internal structures and detecting defects such as porosity, cracks, or incomplete powder fusion in complex geometries. Ultrasonic testing uses sound waves to detect inconsistencies or flaws within the material, while dye penetrant inspection can identify surface-level defects like cracks or pinholes. Ensuring dimensional accuracy is critical in orthopedic implants, where even minor deviations from design specifications can lead to improper fit or function. Techniques such as coordinate measuring machines (CMM) and 3D scanning are employed to compare the printed implant against its CAD model, ensuring that all dimensions are within the specified tolerances. In addition to dimensional accuracy, assessing structural integrity is vital to ensuring that the implant can withstand the mechanical loads it will experience in the body. Finite element analysis (FEA) is often used during the design phase, but physical testing methods such as fatigue testing, tensile testing, and compression testing are employed during the post-processing phase to validate the implant's mechanical performance. In summary, the post-processing of additive-manufactured implants is a multi-step process designed to optimize the functionality, durability, and safety of the final product. Cleaning, heat treatment, surface finishing, and inspection techniques all play essential roles in ensuring that the implant meets the high standards required for medical applications. Each step is tailored to address the specific challenges posed by the material and geometry of the implant, ultimately resulting in a product that is both mechanically robust and biologically compatible.

2.5 CHALLENGES AND FUTURE DIRECTIONS

AM process has rapidly transformed various industries, including the healthcare sector, by enabling the production of complex and customized implants. However, while the potential of this technology is enormous, several challenges remain, alongside a number of critical areas that need to be addressed to fully unlock its promise in implant manufacturing. One of the foremost challenges lies in the material limitations. Although AM can process a wide variety of materials, including metals, polymers, and ceramics, the range of materials approved for medical use is

still limited [62]. The biocompatibility and mechanical properties of these materials must align with the stringent requirements of medical implants. In particular, achieving both biocompatibility and the structural integrity necessary for long-term implant performance remains a significant technical challenge. Moreover, the inconsistencies in material properties between different batches or even within a single printed structure pose reliability concerns. Regulatory hurdles also represent a significant obstacle. The adoption of AM in medical implants necessitates the creation of new regulatory frameworks or the adaptation of existing ones. Traditional methods of certification and approval, which are typically designed for conventionally manufactured implants, do not always fit the AM paradigm. This is because AM allows for personalized implants, meaning that every product can be slightly different. Regulating a technology that produces customized devices on a case-by-case basis is a complex process. Additionally, the process variability inherent to AM leads to significant challenges in producing consistent, high-quality parts. Small deviations in parameters like temperature, powder composition, or laser power can lead to imperfections in the final product. Addressing these issues requires sophisticated monitoring systems and enhanced control over manufacturing parameters. Looking forward, the future directions of AM in medical implants revolve around overcoming these challenges. Advances in materials science, for example, are likely to yield new materials specifically tailored for AM processes. Machine learning and AI-driven process optimization can help reduce variability in the manufacturing process, leading to more consistent outcomes. Moreover, the incorporation of smart implants, which can monitor their own performance post-surgery, may become a key innovation, reducing the need for invasive follow-ups. In summary, while AM has opened up incredible possibilities for implant production, its widespread adoption is hindered by challenges related to materials, process variability, and regulatory frameworks. Addressing these challenges will require coordinated efforts across multiple domains, including materials science, machine learning, regulatory policy, and clinical practice.

2.6 CONCLUSIONS

Pre- and post-processing is a necessary process step in the era of AM for better functioning of the product. Select the right process for the right product for better function and long life of the product needs to be economical and sustainable also. The present chapter helps in knowing the various pre- and post-process for additively manufactured orthopedic implants and whether the process affects its bio-compatibility, corrosion resistance, and wear resistance. Based on the above literature, the following conclusions are made.

- Post-processing is essential for additive-manufactured biomedical implants to achieve optimal and controlled surface roughness, improving their functionality.
- Pre-processing steps are necessary to ensure better dimensional accuracy of implants, facilitate effective post-processing, reduce costs, and enhance the overall efficiency of the manufacturing process.

- The selection of suitable pre- and post-processing methods enhances the biocompatibility of additively manufactured implants, improving their wear and corrosion resistance, thereby extending their lifespan.
- AM, combined with effective pre- and post-processing, significantly contributes to the health sector by enabling the production of complex implants, improving the overall user experience, and ensuring a promising future for medical applications.
- Post-processing, NDT, mechanical validation, and sterilization are crucial to ensuring the implants meet regulatory standards, ensuring safety, and minimizing the risks of rejection or failure in medical use.

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3 Biomedical Standards and Regulations

Bharti Dhaundiyal, Bhanupratap Gaur, Rupesh Ghyar, and Bhallamudi Ravi

3.1 INTRODUCTION

3.1.1 Manufacturing Processes and Materials in Biomedical Devices

Material selection and manufacturing processes are crucial in developing biomedical devices. They impact safety and determine suitability for medical applications. Both manufacturing process and material are important for biocompatibility to avoid adverse events to the users. Traditional manufacturing methods have been the backbone of medical device production for many years. These methods primarily include machining, injection molding, casting and extrusion [1]. They work with various materials used in medical devices. For example, machining produces metal orthopedic implants with high precision. Injection molding is ideal for manufacturing large quantities of plastic components like syringes. Casting is employed to create complex structures like dental crowns, often using ceramics. Meanwhile, extrusion is used in producing consistent cross-sectional shapes, such as catheters from silicon and polyurethane. Overall, traditional manufacturing is most suited for producing standardized mass-produced biomedical devices.

However, these methods have some drawbacks. In traditional manufacturing, mold tooling and process optimization results in limited customization, longer lead times and higher initial costs. The emergence of non-traditional manufacturing methods, like additive manufacturing (AM), enables the creation of custom devices. Although the per-unit cost of AM is relatively higher, it offers shorter lead time without the need for initial tooling cost. AM also supports range of materials, including metal, polymer, ceramic and even bio-tissue. These advances in AM have opened up new possibilities, particularly in the rapidly developing implants and prostheses market [2, 3]. It is significant to note that AM can be used in manufacturing of both standard mass-produced and custom medical devices.

3.1.2 Additive Manufacturing in Biomedical Implants and Prostheses

AM offers versatility in producing both implantable and prosthesis devices for mass-produced and custom applications. Consider an example of a hip implant. AM can create standard hip implant for mass deployment and a custom hip implant tailored to an individual's anatomical need. In this example, the device is considered as implantable prostheses as it replaces a natural body part, the hip joint, to restore its function while being implanted in the body. There are also devices which are

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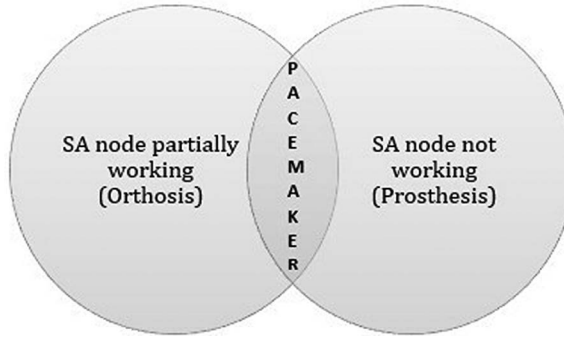

FIGURE 3.1 Overlap in orthosis and prosthesis classification: for example, Pacemaker.

prosthetic but not implantable, for example, prosthetic limbs. In this case, the prosthetic limb is replacing and restoring the function of a lost limb. Additionally, AM can produce devices which are implantable but not prosthetic, for instance, a cranial plate that can fit the general population or be made specifically for individual patient. In this case, a cranial plate is not considered as prosthesis, as it provides only structural support to the brain rather than replacing its function. Devices which provide support, align, correct or enhance the function of a body part are called orthosis [4].

In some cases, a device can overlap as both prosthesis and non-prosthesis (orthosis) depending upon its functionality. Consider a pacemaker, an implantable device to regulate the heartbeat. In case of complete failure of the sinoatrial (SA) node, pacemaker acts as a prosthesis as it replaces the functionality of the SA node completely. Whereas, when SA node is partially working, pacemaker acts as an orthosis where the function of the actual SA node is not replaced but supplemented by the pacemaker in the absence of heartbeat (Figure 3.1).

3.1.3 Standards and Regulations in Biomedical Implants and Prostheses

It is the responsibility of the National Regulatory Body (NRB) to safeguard and enhance public health within its jurisdiction. It ensures that safe, efficient and high-quality medical devices are made available to its population. To achieve this, NRB releases regulations and standards that must be complied by the manufacturer or importer before making the device available in the market. Figure 3.2 illustrates the interaction among various stakeholders involved in bringing a medical device to the market. In the US, the Food and Drug Administration (FDA) serves as the NRB, whereas in India, it is the Central Drugs Standard Control Organization (CDSCO). In the case of the European Union, medical device regulation involves collaboration among the European Commission, national competent authorities, notified bodies and the European Medical Agency (EMA). Regulations made by these NRBs can take the form of the rules, directives, regulations or acts. These regulations are based on risk classification and are mandatory to comply in order to manufacture, sell or import medical devices in the corresponding jurisdiction. Standards, on the other side, may focus on processes and materials and are device specific rather than

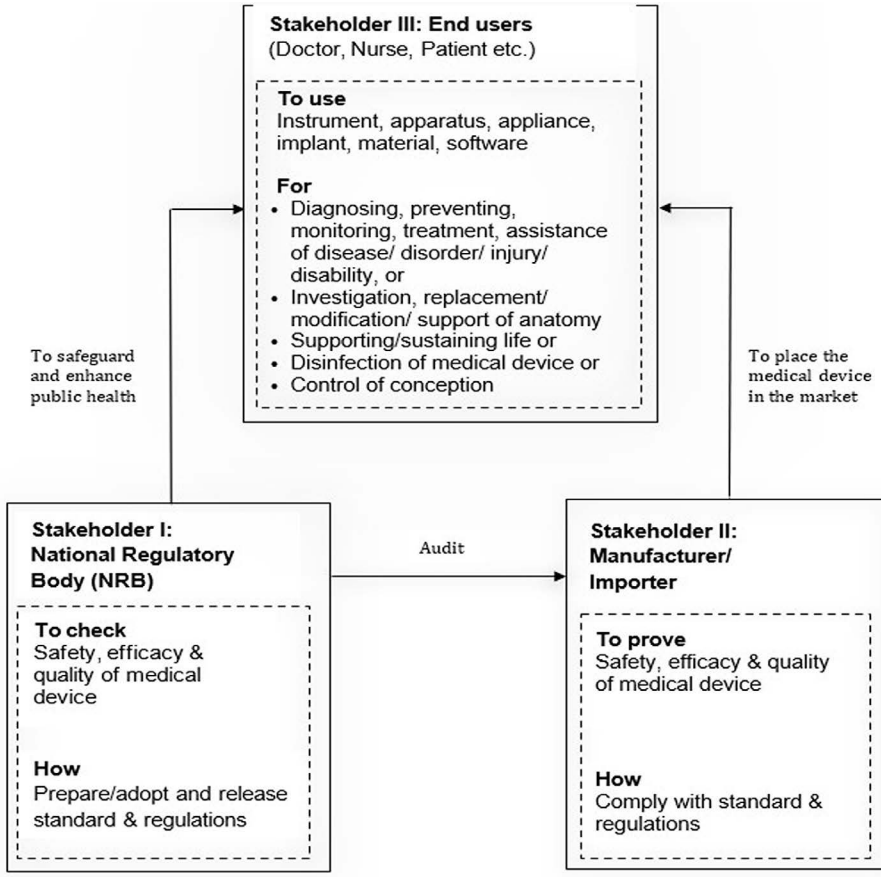
Stakeholder III: End users
(Doctor, Nurse, Patient etc.)
To use
Instrument, apparatus, appliance, implant, material, software
For
• Diagnosing, preventing, monitoring, treatment, assistance of disease/ disorder/ injury/ disability, or
• Investigation, replacement/ modification/ support of anatomy
• Supporting/sustaining life or
• Disinfection of medical device or
• Control of conception
To safeguard and enhance public health
To place the medical device in the market
Stakeholder I: National Regulatory Body (NRB)
To check
Safety, efficacy & quality of medical device
How
Prepare/adopt and release standard & regulations
Audit
Stakeholder II: Manufacturer/ Importer
To prove
Safety, efficacy & quality of medical device
How
Comply with standard & regulations

FIGURE 3.2 Interaction between NRB, manufacturer/importer and end user for placing medical devices into the market.

risk-based classification of the devices. Standards play a significant role in completing the design verification and proving the device is safe, efficient and of high quality to NRB Examples of such standards include the International Organization for Standardization (ISO), the International Electrotechnical Commission (IEC), the American Society for Testing and Materials (ASTM) and the Association for the Advancement of Medical Instrumentation (AAMI).

3.2 STANDARDS ON ADDITIVELY MANUFACTURED BIOMEDICAL IMPLANTS AND PROSTHESES

3.2.1 Standards Based On Design

AM biomedical devices must be verified for safety, efficacy and performance. Design standards are crucial for defining the specifications of finished parts and the tolerances for materials and processes used.

3.2.2 Standards Based On Material and Processes

After adhering to design standards, manufacturers must ensure the safety of the AM process. General process standards such as biocompatibility, sterility and packaging must also be met to prove the AM process is safe for public use.

3.2.3 Standards Based On Test Methods

Post-manufacturing, devices must be tested to conform to the specification outlined in the design standards. These methods provide guidelines for conducting tests such as mechanical assessment, defect detection and post-processing inspections.

Table 3.1 provides a list of the standards, not limited to, that are common for the mass-produced and custom-made AM devices.

TABLE 3.1
Correlation between AM Standards for Design, Process and Testing Methods [5, 6]

Design	Process	Testing Method
1. Common Material Standards: Metals, Polymers, Ceramics		
• ISO/ASTM 52910: Design – Requirements, guidelines and recommendations • ISO/ASTM 52915: Specification for AM file format (AMF) Version 1.2	• ISO/ASTM 52901: General Principles – Requirements for Purchased AM Parts • ISO/ASTM 52902: Test artefacts – Geometric capability assessment of AM systems • ISO/ASTM 52931: AM of metals – Environment, health and safety – General principles for use of metallic materials • ISO/ASTM 52950: Overview of data processing • ISO 17296-2: AM – General principles – Part 2: Overview of process categories and feedstock	• ISO 17295: AM – General principles – Part positioning, coordinates and orientation • ISO/ASTM 52927: General principles – Main characteristics & corresponding test methods
2. Material Standards: Polymers		
• ASTM F3529: Design – Material Extrusion of Polymers • ISO/ASTM 52903-1: Material extrusion-based AM of plastic materials – Part 1: Feedstock materials	• ISO/ASTM 52903-2: Material extrusion-based AM of plastic materials – Part 2: Process equipment	• ASTM F3489: Material Extrusion – Recommendation for Material Handling and Evaluation of Static Mechanical Properties
• ASTM F3091/F3091M-14: Standard Specification of Powder Bed Fusion of Plastic Materials • ISO/ASTM 52911-2: Design – Part 2: Laser-based powder bed fusion of polymers	• ISO/ASTM 52925: Feedstock materials – Qualification of materials for laser-based powder bed fusion of parts	

(Continued)

TABLE 3.1 *(Continued)*
Correlation between AM Standards for Design, Process and Testing Methods [5, 6]

Design	Process	Testing Method
3. Common Material Standards: Metals		
• ISO/ASTM 52907: Feedstock materials – Methods to characterize metallic powders	• ASTM F3049: Standard Guide for Characterizing Properties of Metal Powders Used for AM Processes • ISO/ASTM 52926-1: General Qualification of Operators • ISO/ASTM 52928: Additive manufacturing of metals – Feedstock materials – Powder life cycle management • ISO/ASTM 52935:2023 • AM of metals – Qualification principles – Qualification of coordination personnel	• ASTM F2971: Reporting Data for Test Specimens Prepared by AM • ASTM F3571: Particle Shape Image Analysis by Optical Photography to Identify and Quantify Agglomerates/ Satellites in Metal Powder Feedstock • ASTM F3637: AM of Metal – Finished Part Properties – Methods for Relative Density Measurement
3.1. Common Process Standards: Power Bed Fusion (PBF)		
• ASTM F2924: TI-6Al-4V with PBF or • ASTM F3001: Ti-6Al-4V ELI with PBF or • ASTM F3055-14a: Nickel Alloy (UNS N07718) with PBF or • ASTM F3056: Nickel Alloy (UNS N06625) with PBF or • ASTM F3184: Stainless Steel Alloy (UNS S31603) with PBF or • ASTM F3213: Cobalt-28 Chromium-6 Molybdenum via PBF or • ASTM F3302: Titanium Alloys via PBF	• ASTM F3301: Post Processing Methods – Thermal Post-Processing Metal Parts Made Via PBF • ASTM F3522: Feedstock Materials – Assessment of Powder Spreadability • ASTM F3592: Powder Bed Fusion – Guidelines for Feedstock Re-use and Sampling Strategies • ASTM F3615: Condition-Defined Maintenance for Optical Systems • ISO/ASTM 52904: AM of metals – Process characteristics & performance – Metal PBF process to meet critical applications • ISO/ASTM 52945: AM for automotive – Qualification principles – Generic machine evaluation and specification of key performance indicators for PBF-LB/M processes	• ASTM F3624-23: Measurement & Characterization of Surface Texture • ISO/ASTM 52908: Post processing, inspection & testing of parts produced by PBF

(Continued)

TABLE 3.1 *(Continued)*
Correlation between AM Standards for Design, Process and Testing Methods [5, 6]

Design	Process	Testing Method
3.1.1. Process Standards: Power Bed Fusion-Laser Beam (PBF-LB)		
• ASTM F3318: AlSi10Mg with PBF-LB or • ASTM F3530: Standard Guide for AM – Design – Post-Processing for Metal PBF-LB or • ASTM F3607: Maraging Steel via PBF-LB or • ASTM ISO/ASTM 52911-1: Design – Part 1: PBF-LB of metals	• ISO/ASTM 52926-2: Qualification of Operators for PBF-LB • ISO/ASTM 52930 TS: AM – Qualification principles – Installation, operation and performance (IQ/OQ/PQ) of PBF-LB equipment	• ASTM F3626: Test Artifacts – Accelerated Build Quality Assurance for PBF-LB
3.1.2. Process standards: Power Bed Fusion-Electronic Beam (PBF-EB)		
• ISO/ASTM 52911-3 Design – Part 3: PBF-EB of metallic materials	• ISO/ASTM TR 52917 AM – Round Robin Testing – General Guidelines • ISO/ASTM 52926-3: Qualification of Operators for PBF-EB	• ISO/ASTM TR 52905 AM of Metals – Non-Destructive Testing and Evaluation – Defect Detection in Parts
3.2. Process Standards: Direct Energy Deposition (DED)		
• ASTM F3413: Design – DED	• ASTM F3187: Standard Guide DED of Metals • ISO/ASTM 52926-4: Qualification of Operators for DED-Laser Beam • ISO/ASTM 52926-5: Qualification of Operators for DED-Arc	

Note: In case of standard mass-produced biomedical devices, product-specific standards will also be applicable. However, same is not true in case of custom-made devices.

3.3 REGULATIONS IN ADDITIVELY MANUFACTURED BIOMEDICAL DEVICES

3.3.1 Standard Mass-Produced Device vs Patient-Specific Device vs Custom-Made Device

Regulations for biomedical devices are based on risk classification, regardless of the manufacturing process (such as AM) or type of devices (implants or prostheses). However, the extent of regulatory scrutiny varies between standard mass-produced or custom-made devices. Standard mass-produced devices are manufactured and verified for set range of design specifications. Once approved, these devices are marketed without alteration to their design or performance specifications. The prolonged use of mass-produced devices helps in developing product-specific standards.

Technical committees such as ISO and IEC create these standards, which enhance safety and efficacy of these devices and guide new manufacturers. A patient-specific device is a device which needs adjustment within the scope of existing approval to better fit a patient's anatomical or physiological needs. Hence, the regulatory pathway for these devices differs slightly from that of standard mass-produced devices. This difference typically includes additional documentation or validation to show that the adjustment does not compromise intended use or safety. Additionally, adjustment required for patient-specific devices should be directed by healthcare professionals. In some regions, these are known as patient-matched devices [7–9]. Conversely, devices requiring adjustment beyond the scope of existing approval fall under the category of custom-made devices. Specific country requirements must be met to classify them as custom-made devices; refer to Figure 3.3.

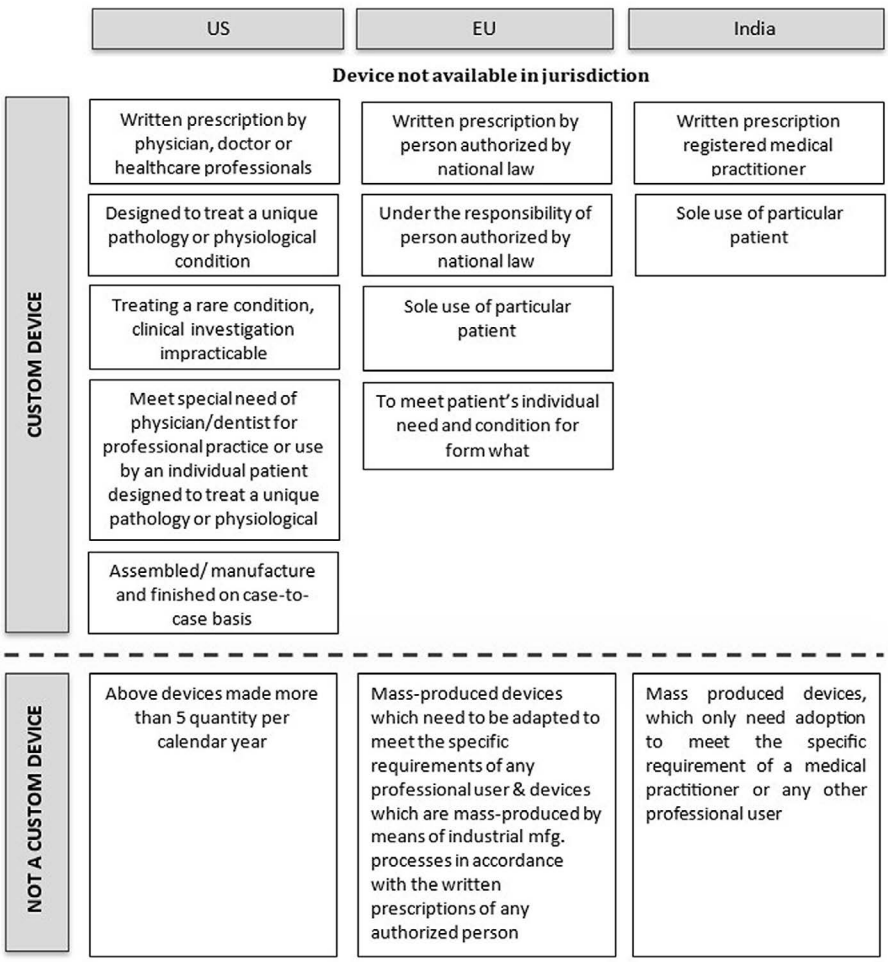
US
EU
India
Device not available in jurisdiction
CUSTOM DEVICE
Written prescription by physician, doctor or healthcare professionals
Written prescription by person authorized by national law
Written prescription registered medical practitioner
Designed to treat a unique pathology or physiological condition
Under the responsibility of person authorized by national law
Sole use of particular patient
Treating a rare condition, clinical investigation impracticable
Sole use of particular patient
Meet special need of physician/dentist for professional practice or use by an individual patient designed to treat a unique pathology or physiological
To meet patient's individual need and condition for form what
Assembled/ manufacture and finished on case-to-case basis
NOT A CUSTOM DEVICE
Above devices made more than 5 quantity per calendar year
Mass-produced devices which need to be adapted to meet the specific requirements of any professional user & devices which are mass-produced by means of industrial mfg. processes in accordance with the written prescriptions of any authorized person
Mass produced devices, which only need adoption to meet the specific requirement of a medical practitioner or any other professional user

FIGURE 3.3 Criteria for categorizing devices as custom-made in the US [10, 11], EU [12] and India [13].

3.3.2 Region-Specific Regulation

3.3.2.1 The US – Food, Drug, and Cosmetic Act

In the US, medical devices are regulated as per the Food, Drug and Cosmetic Act (FD&C Act). They are classified into Class I, II and III based on increasing risk levels. Custom-made devices are exempted from premarket notification (510(k)) and premarket approval (PMA) requirements. However, manufacturers of these devices must still adhere to key FDA regulations, including labeling them "Custom Device". Manufacturers are also required to submit annual reports to the FDA.

The definition of custom-made devices in the US allows for two distinct categories; patient-centric and physician-centric devices [10].

Example 1: Consider a patient for artificial cervical disc replacement. The available sizes of cervical discs do not fit patient's unique spinal dimensions. A custom device is developed specifically to fit this patient's cervical spine, addressing his rare condition.

Example 2: A surgeon in the US with a congenital hand deformity has difficulty in using standard surgical instruments. He works with an AM company to create customized instruments suited to his hand's shape and functionality. These instruments are intended for use only by this surgeon.

In Example 1, the device is a patient-centric made to address rare condition and intended for specific patient. In Example 2, the device is physician-centric, customized for a surgeon's unique needs and used solely in his practice.

3.3.2.2 Europe Union – Medical Device Regulation, 2017/745

In the European Union, medical devices are classified into four risk-based categories; Class I (lowest risk), Class IIa, Class IIb and Class III (highest risk) as per Medical Device Regulation, 2017/745 (MDR 2017/745). The classification determines the regulatory pathway required for market approval. Class I devices are further divided into Class I non-sterile, non-measuring (Class I_{nsnm}) and Class I sterile/measuring/reusable surgical instruments. Class I_{nsnm} are self-certified devices. Class I_{nsnm} products do not undergo review by a notified body. Standard mass-produced devices in Class I sterile/measuring/reusable surgical instruments, IIa, IIb and III must undergo conformity assessment procedure by a notified body. For custom-made devices, only Class III implantable devices require notified body review.

Custom-made devices are regulated under Annex XIII – Procedure for Custom-Made Devices, of MDR 2017/745. Unlike standard mass-produced devices, they do not require CE marking but must be labeled "Custom-made Device". These devices are also exempted from the European Database on Medical Devices (EUDAMED) registration. Manufacturer of custom-made devices has to issue a statement per Annex XIII, instead of the standard Declaration of Conformity (DoC). Data retention period for both standard and custom-made devices is at least 10 years, extending to 15 years for implantable devices.

In addition to custom-made devices, the MDR, 2017/745, also addresses adaptable and patient-matched devices, which are not classified as custom-made. Adaptable

medical devices are mass-produced and adjusted or assembled at the point of care. Such devices are made in accordance with the manufacturer's validated instructions, to suit an individual patient's specific anatomical features. Examples include hearing aids, spectacles, orthotic braces. However, surgical guides based on MR/CT data are patient-matched devices. These devices are tailored to individual patient's needs but still follow standardized manufacturing protocols. Both adaptable and patient-matched devices are designed and produced in consultation with an authorized healthcare professional but under the responsibility of a manufacturer. Both types of the devices must follow a regulatory pathway similar to standard medical devices [7].

3.3.2.3 Indian – Drug and Cosmetic Act, 1940

In India, medical devices are regulated under the Drug and Cosmetic Act, 1940 by the Ministry of Health and Family Welfare. Central Drugs Standard Control Organization (CDSCO) is a regulatory body under the Ministry of Health and Family Welfare for enforcing the Drug and Cosmetic Act, 1940. Recognizing the need for specific regulations to directly address the complexities of medical devices, the Indian Medical Device Rule (IMDR), 2017, was established under the Drugs and Cosmetics Act, 1940. These rules classify medical devices into four categories, A, B, C, and D, based on increasing levels of risk.

As per IMDR, 2017, Indian or overseas manufacturers of mass-produced or standard medical devices must have appropriate license before making it available in the market. Manufacturers should have a test license (Form MD-13) before applying for a manufacturing license. The test license is mandatory before performing any internal/external design verification. Test license is also required in case a manufacturer wants to manufacture device for purpose of clinical investigations, tests, evaluations, examinations, demonstrations or for training purposes. Manufacturing license applications (Form MD-3) for low-risk devices such as Class A and B are managed by the State Licensing Authority. For high-risk Class C and D devices, manufacturing license applications (Form MD-7) are handled by the Central Licensing Authority.

Overseas manufacturers must appoint an authorized agent in India for licensing. Test license application has to be made using test license (Form MD-16), followed by import license application (Form MD-14) for standard mass-produced device. This import license is applicable for all classes of the device and is managed by Central Licensing Authority.

If clinical investigations are needed, Form MD-22 needs to be submitted by Indian/overseas manufacturer followed by Form MD-26 for manufacturing/importing the device that do not have predicate device in India. Overseas manufacturer having free sale certificate issued by the national regulatory authority of the countries, namely, Australia, Canada, Japan, European Union, the UK or the US, can apply for import license without carrying out clinical investigations.

Custom-made devices, including those made using AM, are exempt from test and manufacturing/import licenses in India. Instead, a written prescription from a medical practitioner is required, confirming the device is made under their responsibility for specific patient. These devices must be labeled "Custom Made Device".

Refer to Figure 3.4 for regulatory overview of standard mass-produced devices and Figure 3.5 for custom-made devices in the US, EU and India. Similarities and

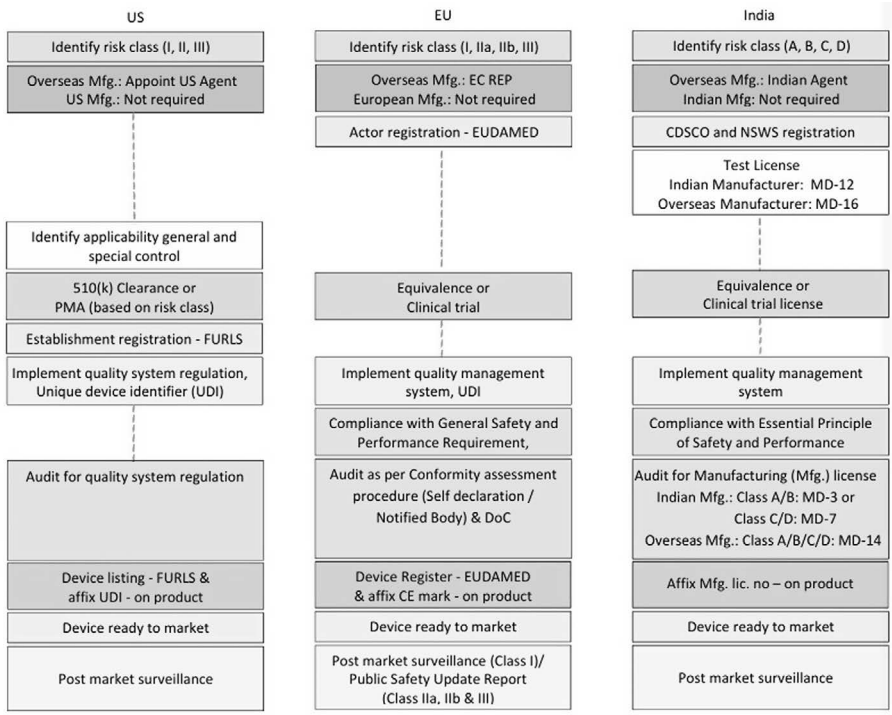
US
Identify risk class (I, II, III)
Overseas Mfg.: Appoint US Agent
US Mfg.: Not required
Identify applicability general and special control
510(k) Clearance or PMA (based on risk class)
Establishment registration - FURLS
Implement quality system regulation, Unique device identifier (UDI)
Audit for quality system regulation
Device listing - FURLS & affix UDI - on product
Device ready to market
Post market surveillance
EU
Identify risk class (I, IIa, IIb, III)
Overseas Mfg.: EC REP
European Mfg.: Not required
Actor registration - EUDAMED
Equivalence or Clinical trial
Implement quality management system, UDI
Compliance with General Safety and Performance Requirement,
Audit as per Conformity assessment procedure (Self declaration / Notified Body) & DoC
Device Register - EUDAMED & affix CE mark - on product
Device ready to market
Post market surveillance (Class I)/ Public Safety Update Report (Class IIa, IIb & III)
India
Identify risk class (A, B, C, D)
Overseas Mfg.: Indian Agent
Indian Mfg: Not required
CDSCO and NSWS registration
Test License
Indian Manufacturer: MD-12
Overseas Manufacturer: MD-16
Equivalence or Clinical trial license
Implement quality management system
Compliance with Essential Principle of Safety and Performance
Audit for Manufacturing (Mfg.) license
Indian Mfg.: Class A/B: MD-3 or Class C/D: MD-7
Overseas Mfg.: Class A/B/C/D: MD-14
Affix Mfg. lic. no – on product
Device ready to market
Post market surveillance

FIGURE 3.4 Regulatory overview of standard mass-produced devices in the US [10, 11], EU [12] and India [13].

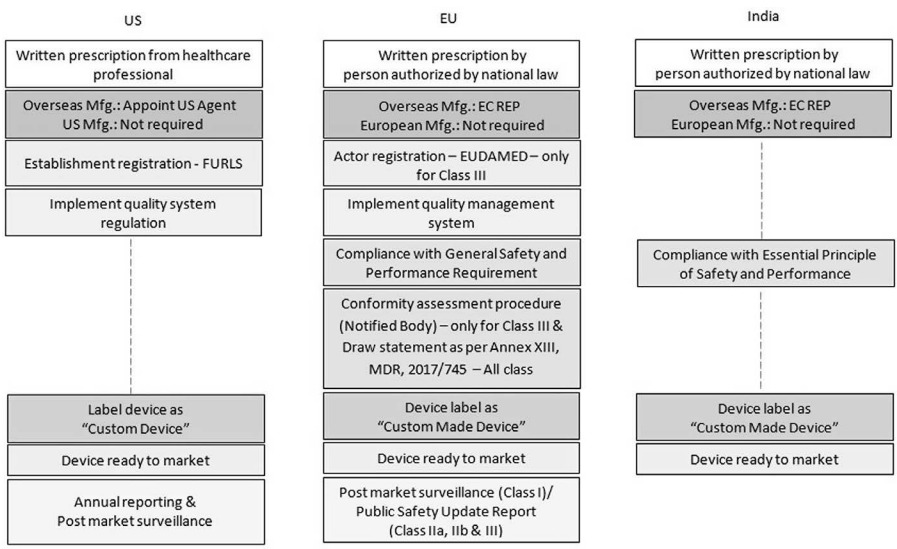
US
Written prescription from healthcare professional
Overseas Mfg.: Appoint US Agent
US Mfg.: Not required
Establishment registration - FURLS
Implement quality system regulation
Label device as "Custom Device"
Device ready to market
Annual reporting & Post market surveillance
EU
Written prescription by person authorized by national law
Overseas Mfg.: EC REP
European Mfg.: Not required
Actor registration – EUDAMED– only for Class III
Implement quality management system
Compliance with General Safety and Performance Requirement
Conformity assessment procedure (Notified Body) – only for Class III & Draw statement as per Annex XIII, MDR, 2017/745 – All class
Device label as "Custom Made Device"
Device ready to market
Post market surveillance (Class I)/ Public Safety Update Report (Class IIa, IIb & III)
India
Written prescription by person authorized by national law
Overseas Mfg.: EC REP
European Mfg.: Not required
Compliance with Essential Principle of Safety and Performance
Device label as "Custom Made Device"
Device ready to market

FIGURE 3.5 Regulatory overview of custom-made devices in the US [10, 11], EU [12] and India [13].

differences between regions, including the requirement for appointing agents and conformity procedures, are highlighted across the three regions.

In Figure 3.4, the process for standard mass-produced devices begins with risk classification and establishment registration (FURLS in the US, EUDAMED in the EU, CDSCO/NSWS in India). Quality management systems are implemented, and audits are required for compliance, followed by device listing in respective databases. Overseas manufacturers need authorized agents for registration in each jurisdiction.

In Figure 3.5, custom-made devices follow a simplified path, often exempt from certain stages but still require registration, quality management and labeling "Custom Made". While custom devices are subject to quality management and post-market surveillance, their regulatory pathway is generally less stringent compared to mass-produced devices, especially for higher-risk categories.

3.4 FUTURE AND CONCLUSIONS

3.4.1 Standards under Development

As the AM field is evolving; industry, regulators and standard setting organizations are collaborating to establish the highest standards of safety and performance in additively manufactured biomedical devices, including implants and prostheses. ISO and ASTM International have signed an agreement to increase their cooperation in developing International Standards for AM. These standards cover aspects such as design, qualification parameters, health and safety, and data packages for AM [14].

3.4.2 Conclusions

This chapter reviewed standards and regulations that apply to AM in biomedical implants and prostheses. Based on it, the following conclusions are made:

- Regulations cover all types of implantable and prosthetic devices made by AM.
- Mass-produced AM biomedical implants and prostheses are subjected to regulations based on risk classification; refer to Figure 3.6.

  Custom-made AM biomedical implants and prostheses are exempt from some regulatory obligations but are not entirely excluded from regulation.
- For AM devices, standards exist for materials, processes, and testing methods rather than product specific. This is because AM is process-oriented technology. Therefore,
  1. Product-specific AM standards for implants and prostheses are less common.
  2. Manufacturers of mass-produced AM implants and prostheses can still use product-specific non-AM standards for design verification.
  3. Manufacturers of custom-made AM implants and prostheses should develop in-house standards for design verification.
- Limited standards exist for ceramic and bioprinting AM products.

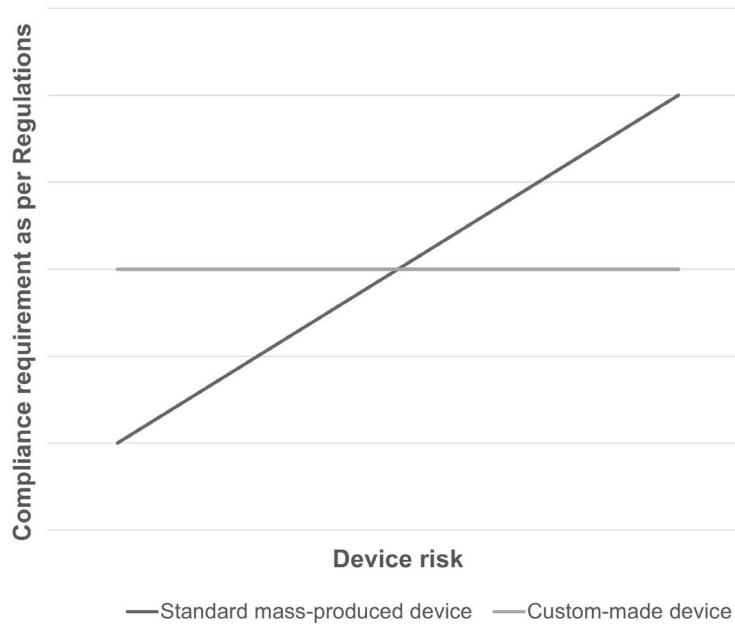

FIGURE 3.6 Compliance requirement for standard mass-produced device vs custom-made device based on device risk classification.

AM offers significant advantages, particularly in the areas of customization, flexibility and speed. However, despite its benefits, manufacturers must strictly adhere to standards and regulations to ensure that the safety and performance of the devices produced through AM are not compromised.

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4 Additive Manufacturing Technologies and Materials in the Fabrication of Personalized Implantable Prosthetics

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4.1 BRIEF HISTORY OF 3D PRINTED IMPLANTABLE PROSTHETICS

The field of three-dimensional (3D) printed medical devices is expanding rapidly, offering technological innovations that address individual needs and provide personalized solutions. The medical application of 3D printing, also known as medical additive manufacturing (AM), has emerged as a significant industry over the last few decades. By creating physical representations based on digital data, this technology enables the versatile fabrication of complex structures such as prosthetics, implants, drug delivery systems, and reconstructed anatomical models. To date, fields such as orthopedics, dentistry, and reconstructive surgery have made effective and practical efforts to integrate 3D implantable prosthetic technology into everyday clinical practice. In the long term, the deployment of this technology has the potential to significantly reshape medical care and improve patient outcomes by enhancing surgical efficiency, accelerating recovery, increasing overall treatment success, and providing personalized care in a cost-effective manner [1–3].

The first 3D photopolymer structures were created by Hideo Kodama and Charles Hull in the 1980s [4–6]. This marked the first time a 3D printer prototype could produce a 3D object with specific colors, textures, and shapes based on instructions from an electronic file (computer-aided design and manufacturing: CAD/CAM files). Hull initially called this method "stereolithography" (SLA) and spent the following years developing the first commercial 3D printer. Recognizing the vast potential of this technology, research and industry in this field have experienced a major boom over the past few decades. Beginning with polymers, techniques for the AM of various materials—such as plastics, metals, and ceramics—were developed in the 1990s, along with different types of 3D printers based on technologies such as SLA,

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selective laser sintering (SLS), fused deposition modeling (FDM), digital light processing (DLP), and PolyJet, to mention a few [7, 8]. In subsequent years, prototypes manufactured using these technologies became widely available and were employed in industries such as aerospace, automotive, and healthcare [9].

Currently, the most promising developments in the field include custom prosthetics, dental and maxillofacial implants, bioprinted tissues as well as surgical instruments and anatomical models for pre-surgical planning and education. Among the first implanted structures were jawbone, spinal, cranial, and hip endoprosthesis implants, each individually manufactured to match the patient's anatomical needs [10]. Key developmental challenges include ensuring biocompatibility and optimizing the strength and durability of the materials [11]. Additionally, surgical planning has benefited from 3D printed prototypes, which have also been integrated into medical training, providing realistic models for manual procedure practice [3, 12].

Efforts in this field also include the development of various types of grafts—such as skin, bone, and blood vessels—which are invaluable in areas like burn medicine [13]. Significant advancements in biocompatibility include surface coatings, improved structural porosity to facilitate osseointegration, the combination of different materials to better mimic human tissues, personalized designs based on imaging data, and advances in sterilization techniques [14]. A parallel effort aims to reduce the associated costs, which is expected to become feasible once the framework and technology are more widely accessible [3].

However, the medical industry, particularly in the area of implantable 3D printed prosthetics, continues to face challenges due to ethical, regulatory, and financial considerations, limiting the widespread adoption of this highly valuable technology. Ongoing challenges related to development and regulation must be addressed before the most groundbreaking applications of this technology can fully mature [3, 15].

4.2 3D PRINTED IMPLANTABLE PROSTHETICS IN CLINICAL APPLICATIONS

3D printing technologies have broad biomedical applications, including surgical visualization, planning and training models, drilling and cutting guides, specialized tools, personalized orthotics, resorbable or permanent implants, and drug delivery devices. The rapid development of this field has led to the availability of low-cost machines, open-source software, and user-friendly interfaces, significantly increasing the popularity of 3D printing.

Despite its advantages, the medical field has been slower to adopt 3D printing for implant production compared to other industries. This delay is largely due to the stringent standards, regulatory challenges, and ethical considerations inherent in medical applications [16–17].

Personalized, custom-made implants tailored to individual patient needs offer several advantages [15, 18, 20, 21]:

- *Adaptability to Complex Cases*: Custom implants are ideal for cases where defects are irregularly shaped and distort normal anatomy.
- *Structural and Functional Compatibility*: These implants can closely mimic the structural and functional properties of the patient's tissue.

- *Reduced Operation Time*: Custom implants minimize the need for intraoperative measurement and trial fitting, reducing operation time.
- *Decreased Use of Heterogenic Grafts*: This leads to reduced costs, time saving, and lower risk of disease transmission.
- *Improved Fixation and Stabilization*: Custom implants provide better primary fixation and stabilization.
- *Enhanced Patient Satisfaction*: Custom implants improve functional outcomes and patient satisfaction.
- *Reduced Waste*: 3D printing is more environmentally friendly compared to traditional subtractive technologies.

However, several limitations remain as follows:

- *Specialized Personnel and Logistics*: Trained professionals and sophisticated logistics are required.
- *Limited Material Options*: Although progress has been made, material choices remain limited.
- *High Costs*: The equipment needed for producing implantable devices is expensive and involves high maintenance costs.
- *Time-Consuming Process*: Planning and manufacturing take significant time, often requiring more involvement from the surgical team.
- *Regulatory and Ethical Challenges*: Regulatory and ethical issues concerning standardization, patient safety, and ethical use must be addressed.
- *Durability and Longevity*: There is limited long-term data on the durability and longevity of these implants.

The time and cost-effectiveness of 3D printed implants depend on specific circumstances and objectives. With an optimized infrastructure, the entire production cycle can be completed within 24 hours [18]. Although this rapid turnaround may not be suitable for acute cases, it is often faster than acquiring specialized implants or shipping them to remote locations. While 3D printed implants may appear more expensive than off-the-shelf products, due to equipment, material costs, and necessary medical work hours; secondary savings—such as reduced operating room time and decreased reliance on heterogenic grafts—make them a viable option.

Despite the challenges, the continuous development of 3D printing is leading to its growing adoption in various medical fields, including (examples on Figure 4.1) the following:

- **Neurosurgery and Spine Surgery** (details below)
- **Orthopedics** (details below)
- **Dentistry** (e.g., dental implants) [22, 23]
- **Cardiology and Heart Surgery** (e.g., valves and vascular grafts) [24, 25]
- **Maxillofacial Surgery** (e.g., skull, palatal- and jaw implants) [26, 27]
- **Otolaryngology** (e.g., ear implants, tracheal splints) [28, 29]
- **Ophthalmology** (e.g., orbital and corneal implants) [30, 31]
- **Plastic and Reconstructive Surgery** (e.g., personalized soft tissue implants) [32, 33]

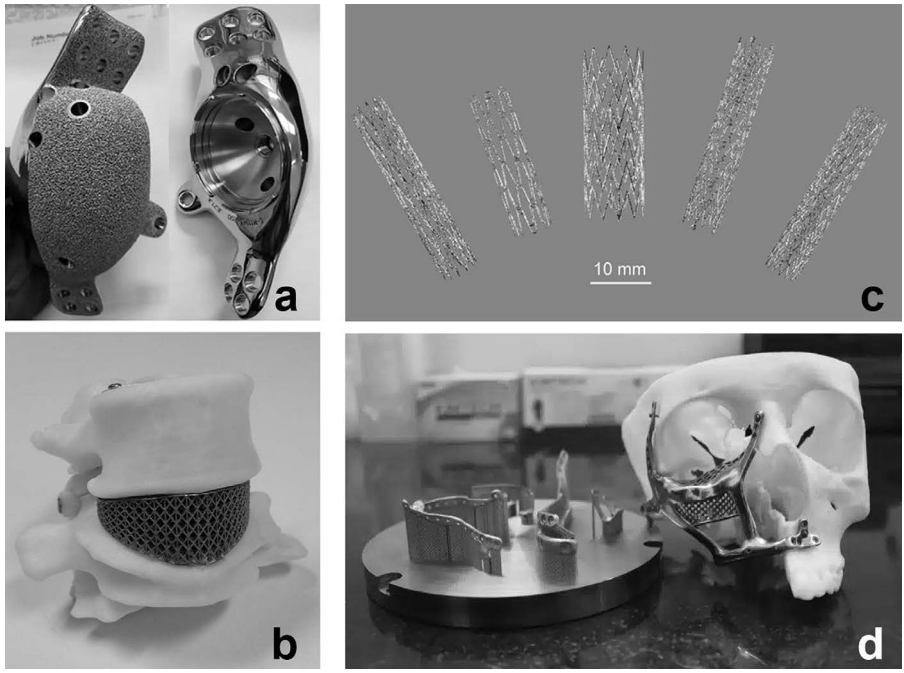

FIGURE 4.1 Examples of 3D printed implantable prosthetics. (a) Custom-made pelvis implant for multiple failed hip replacements; (b) 3D printed vertebral cage; (c) 3D printed nitinol artery stents; (d) custom-made face implant.

Sources: (a) Cleveland Clinic [34]; (b) RMIT Australia [35]; (c) Lab22 Centre for Metallic Additive Manufacturing [36]; (d) Indian Institute of Technology Madras [37].

In summary, while there are limitations and challenges associated with 3D printed implants, their potential for customization and clinical benefits are driving increased adoption across multiple medical specialties.

4.2.1 Neurosurgery and Spine Surgery

With the simultaneous advancement of imaging technologies and AM, the use of 3D printing in neurosurgery has evolved from printed models and preoperative planning to patient-specific implant production, especially in spinal surgery and cranioplasty. In spinal surgery, 3D printed implants aim to restore stability with advantageous biomechanical profiles following degenerative diseases, malignancies, or traumatic injuries [38]. For spinal implants, the two most frequently used materials are porous titanium alloys and polyether ether ketone (PEEK) [39, 40].

Since 2016, 3D printed spinal implants have been used in all spinal regions with good efficacy, focusing on patient mobility, implant migration, reoperation rates, and bone ingrowth for long-term stabilization (osseointegration). Only a few cases have reported inflammatory or migration complications [38, 40]. Many FDA-approved off-the-shelf 3D printed titanium alloy implants are available in various sizes

and angles (e.g., EIT Cellular Titanium®, Stryker Tritanium®), simplifying logistics without the need for setting up a 3D printing laboratory [38]. Patient-specific 3D printed spinal implants are predominantly used in cancer patients, where the resection cavity requires individualized solutions, resulting in reduced operation times, lower complication rates, and better functional outcomes [23]. Titanium implants are generally superior to PEEK devices in terms of osseointegration, while PEEK implants tend to form biofilms that can result in pseudoarthrosis, although PEEK has advantages in radio-opacity for follow-up imaging [38–40].

Craniectomy is performed to relieve increased intracranial pressure, and cranioplasty restores the removed skull segment to reestablish neurophysiologic functions and achieve cosmetic outcomes. Studies have shown that custom-made 3D printed cranioplasty implants are safe, offer satisfactory cosmetic results, and decrease operation times [41, 42]. Newer 3D printed cranioplasty prosthetics made from titanium, PEEK, or polymethylmethacrylate (PMMA) have improved cosmetic outcomes [42–44]. Personalized titanium implants with calcium edges have been successfully used to address complications, such as infections from conventional PEEK or autologous bone grafts, though follow-up periods remain limited [45].

As 3D printing and material science continue to evolve, the field of implantable 3D printed devices is projected to grow by roughly 30% annually through 2026 [39]. The next generation of 3D printed implants will likely include surface modifications, tissue engineering solutions, and drug delivery systems (e.g., growth factors) that enhance osseointegration and decrease complications [46]. While personalized implants have significant potential in reconstructive surgery, further research in material science, particularly regarding sterilization, and more comprehensive clinical validation are needed to ensure their long-term success.

4.2.2 Orthopedics

Given the frequent need for implants in many orthopedic interventions, this field has pioneered the use of 3D printed implants. In joint surgeries, 3D printing has been used to produce customized acetabular reconstruction rings [47], custom cages [48, 49], acetabular cups [50, 51], metaphyseal cones [52, 53], knee prostheses [54], and ankle prostheses [55, 56]. In orthopedic oncology, 3D printing has been employed to create pelvic implants [57–59] and tibial blocks [60]. In trauma surgeries, 3D printed implants offer numerous advantages and have been used to produce blocks or bone reconstruction systems for bone loss [61–64], total talus replacements [65, 66], and custom-made plates [54, 67].

4.3 ADDITIVE MANUFACTURING TECHNOLOGIES IN THE FABRICATION OF PERSONALIZED PROSTHETICS

In the 2000s, the AM industry experienced rapid growth and development [68]. The introduction of new printing technologies and the decrease in printer costs facilitated the expansion of 3D printing in healthcare, including prosthetic production.

In response to this trend, the International Organization for Standardization (ISO) and the American Society for Testing and Materials (ASTM) established the

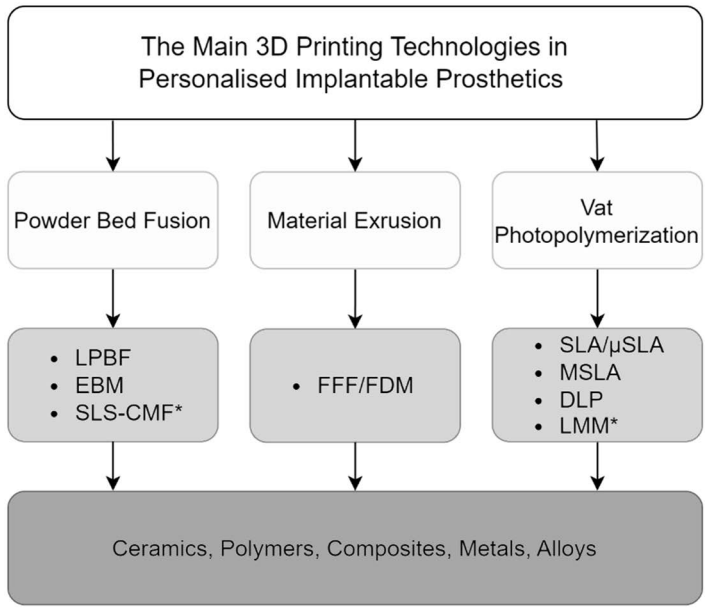

FIGURE 4.2 The most important additive manufacturing techniques for medical applications. The light-gray color indicates the process categories according to ISO 52900. The blue color indicates industrial designations: (Laser Power Bed Fusion = LPBF, Electron Beam Melting = EBM, Selective Laser Sintering-Cold Metal Fusion = SLS-CMF, Fused Filament Fabrication/Fused Deposition Modeling = FFF/FDM, Stereolithography = SLA, Masked Stereolithography = MSLA, Digital Light Processing = DLP, Lithography-based Metal Manufacturing = LMM), and the red color indicates printable materials. The asterisk denotes that this technology requires sintering as a post-processing step.

ISO/TC 261 Technical Committee in 2011 [69] and the ASTM Committee F42 in 2009 [70], both tasked with developing and structuring AM standards. As a result, the number of AM standards grew exponentially in the 2010s.

The ISO/ASTM 52900 standard provides a framework for the terminology used in AM, which this chapter adheres to, but only in the context of personal implantable prosthetics [71]. The primary technologies used in the medical industry are shown in Figure 4.2 and Table 4.1.

4.3.1 Powder Bed Fusion (PBF)

Powder bed fusion (PBF) is a 3D printing process in which a heat source melts powder particles to create layers. A thin layer of powder is spread across the build platform, and specific points are fused using energy, typically from laser. This process is repeated to form the entire object, which is embedded in a bed of unfused powder [71]. The types of the process are shown in Figure 4.3.

The medical industry often requires high-performance or specialized materials. Metal sintering offers a unique advantage by creating parts unattainable through

TABLE 4.1
Comparing the Most Important Additive Manufacturing Techniques for Medical Applications

	Advantages	Disadvantages	Printing Resolution (μm)	Printers
LPBF/SLM/ DMLS	No need for support, high accuracy, does not require much post-processing	High surface roughness and residual stress, requires a supply of inert gas, expensive	20–200	EOS M290, Farsoon FS271M, HBD 400, 3D Systems DMP Flex 350
EBM	No need for support, no oxidation and residual stress	Highly expensive and energy intensive	50–150	Sailong-T200
SLS-CMF	Polymer-based SLS printers can be upgraded to metal printers	Unlike other powder bed fusion printers, it requires a washer and sinter unit	50–150	Nexa3D QLS230
FFF/FDM	Typically the lowest cost printers	Not as dimensionally accurate as other processes, in medical applications currently limited to polymers	100	Orion AM M150, 3D Systems EXT 220 MED
SLA	More detailed prints than other VPP technologies	Printing speed depends on the model size, only suitable for polymer parts	25	Formlabs Form 3BL
MSLA & DLP	Printing speed is independent from the model's horizontal extension	Typically lower resolution than SLA, only suitable for polymer parts	25	Nexa3D XIP Pro Resin & B9Creations Elite Micro Resin
LMM	High-quality finish with fine tolerances	Smaller build volume	40	Holo H200, Incus Hammer Pro40

traditional metalworking methods. For example, titanium alloys can be modeled and printed to create custom prosthetics to replace bone lost due to injury or disease. These prosthetics provide exceptional strength, biocompatibility, and a porous structure that promotes bone ingrowth [72].

4.3.1.1 Laser Powder Bed Fusion (LPBF)

Laser powder bed fusion (LPBF), also known as selective laser melting (SLM) or direct metal laser sintering (DMLS), is a precise 3D printing technique used to create complex metal parts, including medical implants. The process begins by spreading a thin layer of metal powder over a build plate. A laser or multiple lasers trace and fuse the powder according to the design. The build platform lowers after each layer, repeating the process until the object is fully formed. The build chamber is sealed and often

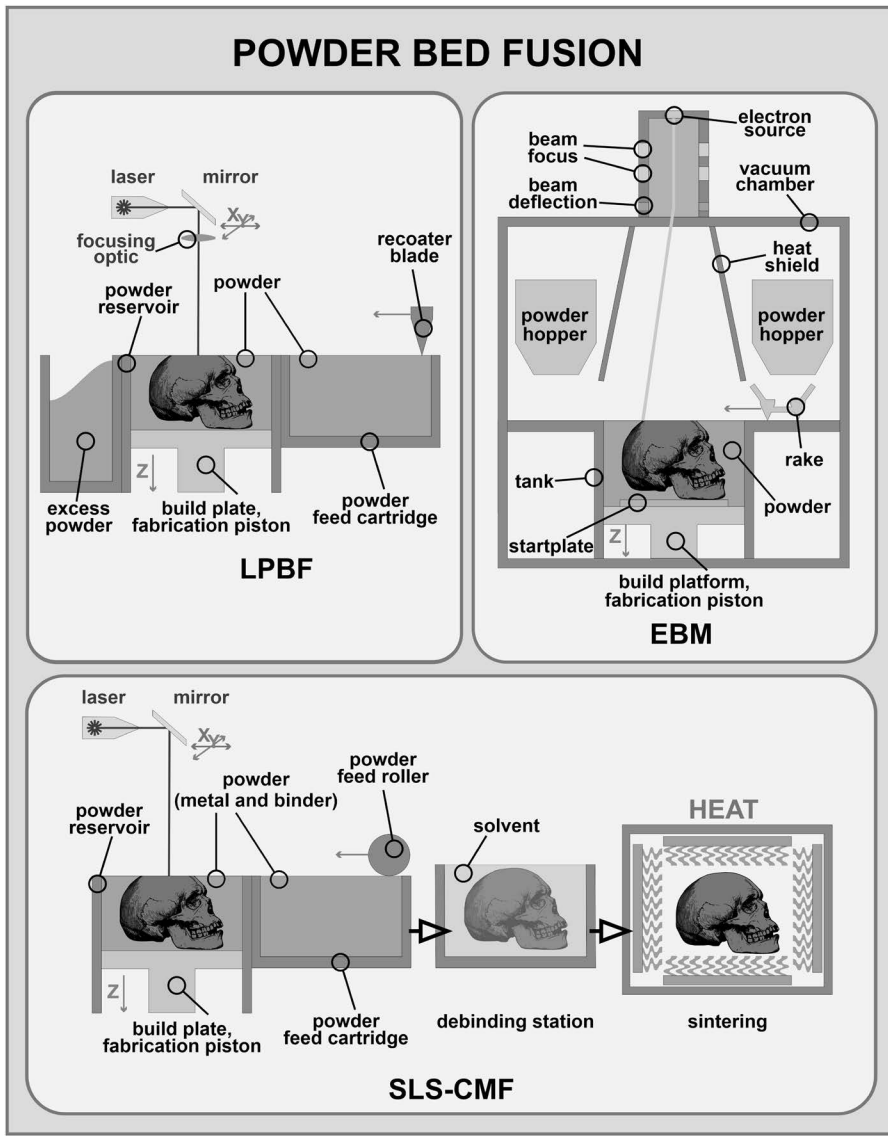

FIGURE 4.3 General principles and workflow of powder bed fusion process. Laser Power Bed Fusion = LPBF, Electron Beam Melting = EBM, Selective Laser Sintering-Cold Metal Fusion = SLS-CMF.

filled with inert gases, such as nitrogen or argon, to prevent oxidation during printing and minimize debris. While the surrounding powder offers some support, additional structures are typically used to ensure part integrity. Once printing is complete, parts are removed, cleaned, and often undergo secondary heat treatment to relieve internal stresses. Unused powder is recovered and recycled for future printing [72, 73].

4.3.1.2 Electron Beam Melting (EBM)

Electron beam melting (EBM) is a metal 3D printing technique similar to LPBF, but it uses an electron beam instead of laser. It is frequently used to manufacture titanium orthopedic implants. EBM is preferred over laser-based methods in certain cases due to its ability to generate more power and heat, making it suitable for specific metals and demanding applications. EBM operates in a vacuum chamber to prevent beam scattering, with chamber temperatures reaching 1,000°C or higher. Electromagnetic control of the electron beam allows it to move faster than laser and even exposes multiple areas simultaneously. EBM typically produces thicker layers and less detailed surface features compared to laser methods. However, due to high build temperatures, EBM parts generally do not require post-print stress relief [74].

4.3.1.3 Selective Laser Sintering-Cold Metal Fusion (SLS-CMF)

SLS typically uses lasers to sinter powdered plastic into 3D shapes by heating polymer particles layer by layer. Cold metal fusion (CMF) adapts this process for metal parts. Unlike traditional SLS, CMF operates at lower temperatures (below 80°C) and sinters only the polymer binder, not the metal powder. SLS machines used for CMF require adjustable parameters tailored to the metal feedstock. As each layer is completed, a new layer of feedstock is applied, and the process repeats without needing support structures.

The resulting green part consists of a plastic matrix filled with metal powder, which can be cleaned, depowdered, and even machined before the final sintering process, at which point it becomes the brown part. The strength of the green part enables automated cleaning with water or compressed air, and unused feedstock can be reused. After chemical debinding removes most of the polymer, the part is finally sintered to form a full metal component [74].

4.3.2 Material Extrusion (MEX)

Material extrusion (MEX) is a versatile 3D printing method commonly used to create objects from polymeric materials. It involves extruding heated material through a nozzle and depositing it layer by layer onto a build platform [71]. The process is shown in Figure 4.4.

4.3.2.1 Fused Deposition Modeling (FDM)

FDM, also known as fused filament fabrication (FFF), was the first commercially available MEX process. In this method, a thermoplastic filament is fed through a heated nozzle, where it melts and is deposited layer by layer onto a build platform. FDM is widely accessible, low-cost, and simple, making it suitable for various materials. In implantable prosthetics, PEEK is commonly used, especially for dental implants, due to its biocompatibility, temperature tolerance, and excellent long-term mechanical properties [75].

While FDM offers versatility and affordability, it has limitations. Printed parts may exhibit lower accuracy, and mechanical properties can vary depending on the

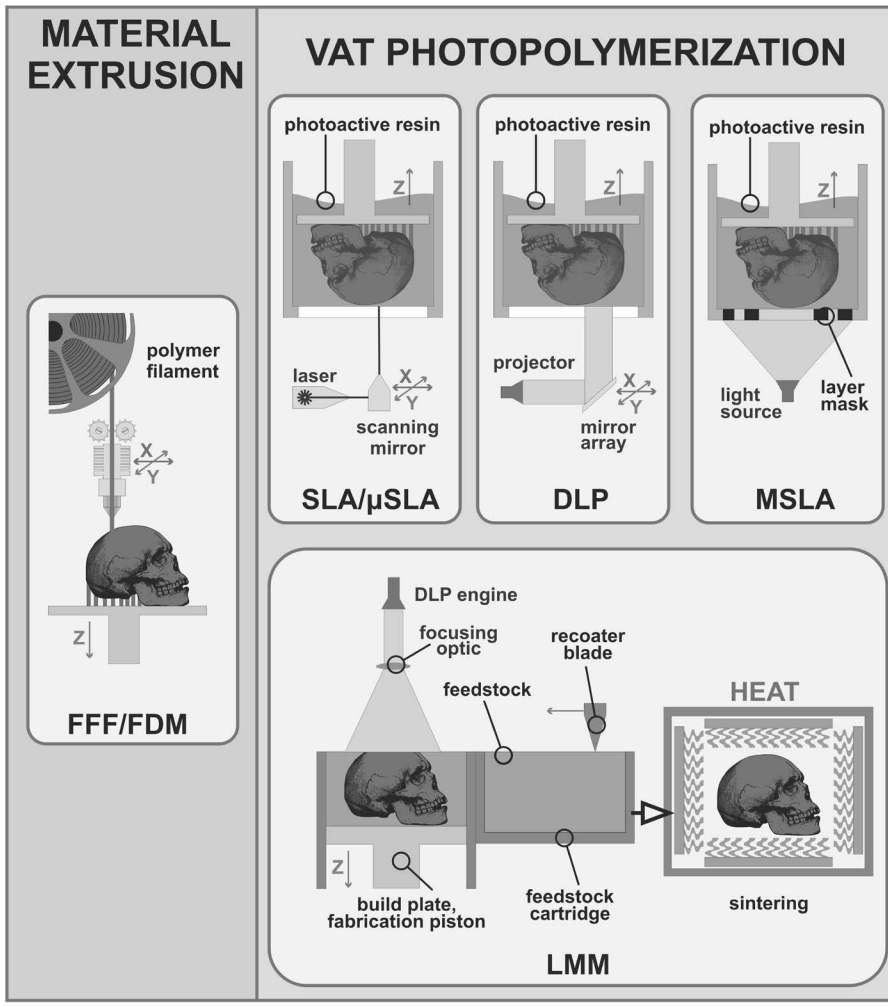

FIGURE 4.4 General principles and workflow of material extrusion and vat photopolymerization processes. Fabrication/Fused Deposition Modeling = FFF/FDM, Stereolithography = SLA, Masked Stereolithography = MSLA, Digital Light Processing = DLP, Lithography-based Metal Manufacturing = LMM.

print orientation. Layer lines may result in weaker regions within the final product, and post-processing steps such as sanding or smoothing are often required to achieve the desired surface finish [76, 77].

4.3.2.2 Bioprinting

Bioprinting utilizes organic or biological materials, such as cells and nutrients, to create living tissues. While it has significant future potential and is undergoing clinical trials, it is not yet a common practice in implantology [78].

4.3.3 Vat Photopolymerization (VPP)

Vat photopolymerization (VPP), also known as resin 3D printing, uses photoreactive materials that solidify when exposed to light. This technology primarily prints polymers. The three main VPP techniques are stereolithography (SLA), masked stereolithography (MSLA), and DLP. SLA uses a UV laser to cure material point by point, MSLA employs a larger UV source masked by an LCD screen for selective curing, and DLP uses a projector to cure an entire illuminated layer at once. These VPP methods are widely used in dental applications, such as producing dental aligners, temporary restorations, and permanent crowns [79]. The types of the process are shown in Figure 4.4.

4.3.3.1 Lithography-Based Metal Manufacturing (LMM)

Lithography-based metal manufacturing (LMM) is a stereolithography-based process that uses photopolymerization to build metal parts layer by layer. Unlike traditional VPP, the starting material is a metal-filled organic binder. This material remains solid at room temperature but liquefies under heat, allowing precise coating of the build platform. Each layer is selectively cured by light exposure, while excess material solidifies by cooling, eliminating the need for support structures. After printing, parts are removed, and unused feedstock can be recycled. Final steps include debinding and sintering, which convert the "green" parts into dense metal components [80]. This technology is commonly used for titanium dental implants.

4.4 MATERIALS USED IN ADDITIVE MANUFACTURING OF IMPLANTABLE PROSTHETICS

4.4.1 Metals and Alloys

Metals are the most commonly chosen materials for implants due to their long-term stability under in vivo conditions and their high mechanical strength [18]. Additionally, metals have gained a strong foothold in the AM of customized medical devices, with several clinical trials and product developments underway.

The most frequently used metal for 3D printed implants, especially in orthopedics, maxillofacial, and dental applications, is titanium and its alloys [48, 52, 81]. Titanium (Ti) and its alloys are renowned for their excellent biocompatibility, lightweight structure, superior tensile strength, and corrosion resistance compared to stainless steel (SS) and cobalt-chromium (CoCr) alloys [82, 83]. It is also worthy to mention that titanium does not interfere with MRI imaging [18]. The most commonly used titanium alloy in AM technologies is Ti6Al-4V [84].

SS is another widely used alloy for the production of surgical implants and instruments. Austenitic SS 316L is a bioinert, readily available, and relatively inexpensive material with good mechanical properties [85]. Additively manufactured SS is primarily used for temporary devices, bone plates, and fracture fixation [18, 86, 87].

Cobalt-chromium alloys are particularly valuable in high-load areas and wear-and-tear applications due to their high strength, corrosion resistance, and wear

durability [88–91]. CoCr alloys have been extensively investigated for use in personalized implant manufacturing, particularly in restorative dentistry and orthopedic surgery [88].

Tantalum, another noteworthy material, exhibits excellent biological inertness and corrosion resistance. It can be produced in a porous form using AM techniques and is used as an implant material or coating for bone and joint regeneration [92–94].

Shape-memory alloys, particularly nickel-titanium (NiTi), are also drawing attention for biomedical implants. NiTi alloys' superelasticity and shape-memory characteristics allow them to return to their original configuration when exposed to heat or mechanical stress, making them ideal for applications such as stents and orthopedic implants [95].

4.4.2 Polymers and Polymer Composites

Polymers and polymer composites are among the most commonly used materials in 3D printing, with polycaprolactone (PCL), polylactic acid (PLA), and polyamide (PA) frequently applied in biomedical fields. Advances in medical imaging, image-editing software, and 3D printing technologies enable the design of customized implants that can precisely replicate missing body parts [96].

Polymers hold significant promise for future use in implantable prosthetics. Studies on polymers, in vitro [97, 98], as well as animal [98, 99], and cadaveric studies [100] have shown promising results. Polymers can be biocompatible [101], biodegradable at varying rates [102], and can offer mechanical properties that can be tailored to match those of human tissues [103], helping to eliminate issues such as stress shielding in bone implants [104]. Incorporating additives into polymers can further enhance their functionality, improving properties such as biocompatibility, cell viability, tissue ingrowth, and proliferation. Materials such as hydroxyapatite (HA) and beta-tricalcium phosphate (β-TCP) have been shown to increase bone cell proliferation and osteogenesis on 3D printed scaffolds in vitro and in vivo [89, 105]. Moreover, AM allows precise control over the porosity of implants, which has been shown to positively affect cell proliferation and vascularization [106].

Despite these advantages, the use of polymers in 3D printed prosthetics is still limited due to cytotoxicity concerns [107], inadequate biodegradability [108], and regulatory challenges for human use [109]. As a result, few clinical studies and trials have been conducted using polymers and polymer composites.

One of the most widely used polymers in implantable prosthetics is polycaprolactone (PCL), a synthetic polymer known for its excellent biocompatibility (it does not induce inflammations of immunological origin) [102, 110], good biodegradability, and excellent mechanical properties [101]. PCL has been used to 3D print scaffolds for maxillary bone reconstruction [111] and orbital mesh implants for repairing orbital fractures [112]. Adding hydroxyapatite (HA) to PCL in the PCL/HA composite was used to enhance bone growth within the 3D printed patient-specific scaffolds for craniofacial defect repair [113], or to enhance mechanical properties of 3D printed splints via SLS to treat tracheobronchomalacia [114].

Photopolymers have also been utilized for implantable prosthetics. Photopolymers are polymers whose structure or chemical properties change upon exposure to specific wavelengths of light [115]. A liquid photopolymer was used to 3D print orbital implants using multi jet fusion technology as part of rehabilitation following evisceration of blind, painful eyes [116]. PEEK , a non-resorbable polymer with adequate mechanical strength and biocompatibility [104], was employed to 3D print an extensive implant for complex anterior chest wall reconstruction via FFF technology [117], yielding satisfactory postoperative outcomes.

A PA/HA composite was successfully used to reconstruct the mandibular condyle following a failed angular mandible ostectomy [118]. Additionally, another PA composite, combined with bioactive glass, was successfully applied in upper craniofacial reconstruction surgeries, with a prolonged follow-up period [119].

3D printed polymers and polymer composites represent promising materials in the field of implants. In vitro, in vivo, cadaveric, and clinical studies using these materials have demonstrated significant success, suggesting the potential for their extensive future application.

4.4.3 Ceramics

Ceramics are versatile materials with significant potential for medical applications. They offer excellent thermal and chemical stability, biocompatibility, corrosion resistance, resistance to wear-and-tear, perfect electrical, optical, and magnetic performance, and mechanical strength, making them ideal for 3D printed implantable prosthetics [120–122]. Ceramic materials were first used in total hip arthroplasty [123].

Ceramics used in biomedical applications can be classified into bioactive ceramics (e.g., wollastonite, bioglass, phosphates, and hydroxyapatite), bioinert ceramics (e.g., zirconia, alumina, and titania), and composite materials. Over recent decades, 3D printed ceramic scaffolds have been used in a variety of biomedical applications. In traditional methods mainly ceramic-based scaffolds, we developed using, leaching, solvent casting, lyophilization, hydrogel formation, and electrospinning [124].

Ceramics commonly used in AM for implant development include alumina (Al_2O_3), zirconia (ZrO_2), hydroxyapatite (HA), silicon nitride (Si_3N_4), and tricalcium phosphate (TCP) [125–129]. Alumina is valued for its hardness, corrosion resistance, and good biocompatibility, making it suitable for load-bearing prostheses such as inserts and heads in knee and hip replacements, though it is brittle [123, 129]. Zirconia, known for its high fracture toughness and wear resistance, is used in dental and orthopedic implants but may undergo phase transformation, which can lead to volume changes [128]. HA mimics the properties of bones; it is highly bioactive and biocompatible and promotes osseointegration. HA is frequently used to coat metal implants and as scaffolds for tissue engineering and bone grafts, although its mechanical strength is limited [127].

Silicon nitride is appreciated for its wear resistance, high fracture toughness, and antibacterial properties, while tricalcium phosphate supports bone regeneration due

to its biodegradability and biocompatibility. Silicon is applied for spine implants, knee and hip replacements [125, 126, 130].

Since cutting ceramic materials is challenging, AM is the preferred method for producing medical implants. In the 1990s, the first reports of 3D printing ceramics were made by Marcus et al. and Sachs et al. [131, 132]. Powder-based 3D printing methods have proven most suitable for developing patient-specific ceramic implants. Ceramic 3D printing technologies include slurry-based methods (e.g., DLP, SLA), powder-based methods (e.g., SLS, SLM), and bulk solid-based methods (e.g., FDM). The most appropriate method for ceramic 3D printing is SLS, as sintered bioceramic implants offer good mechanical strength and are considered biologically active [122]. Mark Schult et al. used the SLS method to develop barium titanate ceramics for bone regeneration via electrical stimulation [133].

In summary, ceramics, polymers, and metals, alongside their alloys and composites, are playing an increasingly important role in the AM of implantable prosthetics. These materials offer a wide range of advantages, from biocompatibility to mechanical strength, but further research and development are needed to overcome existing limitations and ensure broader clinical application. Table 4.2 provides a brief overview of different 3D printing methods for different materials or material composites and their medical applications.

TABLE 4.2
Different 3D Printed Materials/Material Composites and Their Applications in Implantable Prosthetics

	Material/Composite	Abbreviation	3D Printing Process	Application	Reference
Metals and alloys	Titanium (Ti-6Al-4V)	Ti (Ti64)	PBF, VPP	Orthopedic implants, neurosurgery, maxillofacial and dental implants	[48, 52, 84]
	Stainless steel	SS	PBF, MEX, VPP	Temporary implantable devices, fracture fixation, bone plates	[85–87]
	Cobalt-chromium	CoCr	PBF, VPP	Dental implants, high load-bearing orthopedic implants	[90, 91]
	Tantalum	Ta	PBF, VPP	Orthopedic implant, especially bone or joint regeneration	[53, 92–94]
	Shape-memory alloys (Nickel-Titanium)	NiTi	PBF, VPP	Superelastic orthopedic implants, stents	[95]

(Continued)

TABLE 4.2 *(Continued)*
Different 3D Printed Materials/Material Composites and Their Applications in Implantable Prosthetics

	Material/Composite	Abbreviation	3D Printing Process	Application	Reference
Polymers and Polymer Composites	Polycaprolactone	PCL	MEX	Tissue engineering, facial bone reconstruction	[97, 111, 112]
	Polycaprolactone/ hydroxyapatite	PCL/HA	MEX, PBF	Craniofacial defect repair, stents for tracheobronchomalacia	[113, 114]
	Polycaprolactone/ tricalcium Phosphate	PCL/β-TCP	MEX	Facial bone grafts, scaffold material	[130]
	Poly(propylene fumarate)	PPF	VPP	Bone tissue engineering	[98]
	Polylactic acid/ hydroxyapatite	PLA/HA	MEX	Bone tissue engineering	[100, 134]
	Polyether ether ketone	PEEK	MEX	Anterior chest wall reconstruction	[117]
	Nanoscale polyamide/ hydroxyapatite	n-PA/HA	VPP	Mandibular condyle reconstruction	[119]
	Polyamide/bioactive glass	PA/BG	PBF	Craniofacial reconstruction	[118]
Ceramics	Alumina	Al_2O_3	VPP	Dental implants, hip and knee prostheses, cellular cubes, gears	[135]
	Zirconia	ZrO_2	VPP	Femoral heads and dental implants – mandibular molar crowns	[136]
	Silicon nitride	SN	PBF	Applied in joint replacements, dental applications, spinal implants	[137]
	$CaOSiO_2$-P_2O_5-B_2O_3 glass-ceramic	BGS-7	MEX	Reconstruction of zygomatic bone defects	[138]
	Hydroxyapatite/ β-tricalcium Phosphate (OSTEON 3D)	HA/β-TCP (60/40)	VPP	Bone regeneration for implant installation following tooth extraction due to alveolar bone resorption (dental)	[139]

4.5 THE FUTURE OF ADDITIVE MANUFACTURING IN IMPLANTABLE PROSTHETICS

With ongoing advancements in manufacturing technologies, materials science, and personalized medicine, significant progress has been made toward the development of implantable prosthetics with enhanced functionalities [140, 141]. Current primary objectives in this field include reducing the risk of postoperative infections, host-versus-graft reactions, skin complications, and, in the case of bone implants, peri-implant fractures or loosening. Additionally, improving osseointegration and biocompatibility, maintaining biomechanical integrity, and reducing overall manufacturing costs are critical to alleviate the burden on healthcare systems [3, 14, 142].

4.5.1 4D Printing and Its Potential in Prosthetics

4D printing introduces objects that can change in size, shape, color, and function in response to external stimuli, such as changes in pH, humidity, light, water, or electromagnetic fields. The fourth dimension refers to "time," based on the concept first introduced by S. Tibbits in 2013 [140, 143]. Common materials for 4D printing include shape-memory polymers (SMPs), shape-memory alloys (SMAs), hydrogels, and biological structures [140, 143–145]. 4D printing uses established AM techniques, such as FFF, material jetting, and stereolithography [140].

Recent studies have demonstrated that 4D printed, photothermally responsive shape-memory bone tissue implants form rapidly and effectively when exposed to near-infrared radiation [146]. This technology has been successfully tested in rat models with cranial defects, showing improved bone regeneration. Future applications may include self-repairing or self-assembling prosthetics [146–148]. Current research is focused on developing tracheal and vascular stents with shape-memory capabilities and controllable dimensions to enhance precision and effectiveness during and after surgical interventions [148, 149]. Promising results have also been reported from composite-based 4D printing of orbital stents, leading to favorable postoperative outcomes. However, despite these encouraging findings, extensive preclinical and clinical investigations are still required to ensure patient safety before 4D printing can be integrated into clinical practice.

4.5.2 Surface Modifications and Nanocomposites

Ongoing and future research on surface modifications for implants is focused on the development of new biomaterials, coatings, and surface treatments. Nanocomposites, which consist of a matrix material combined with nanoscale fillers (e.g., carbon nanotubes, nanoclay, metals, metal oxides, and hydroxyapatite), are of particular interest [150]. Polymer-based nanocomposites are predominantly used in implantology due to their favorable biological and mechanical properties [150]. Adding fillers to the base material can enhance biocompatibility, impart antibiotic effects, improve mechanical stability, and reduce wear [150]. Surface modification techniques such as nanopatterning can be achieved through mechanical methods like

blasting, grinding, and polishing, or via chemical treatments, including micro-arc oxidation, sonochemical treatment, electron beam physical vapor deposition, and SLM [151]. These technologies can be combined to create surfaces with advanced properties.

4.5.3 Smart Sensors in Implantology

Sensors are increasingly important in biomedicine, and smart sensors are used across various disciplines to measure, analyze, and report data to physicians, providing real-time information on a patient's condition. In implantology, smart sensors have been successfully applied for postoperative monitoring, detecting stress and strain patterns at potential failure sites in traumatology applications, tracking movement, and monitoring implant performance and load-bearing capacity [152, 153].

Electronic printing using multi-material high-resolution jetting technology, such as Nano Dimension's DragonFly printer series, offers innovative possibilities in the development of electronic hardware for medical applications. In the future, this technology could enable the precise 3D printing of complex, multi-layered electronic components such as sensors directly into medical devices, creating compact, customized, and highly integrated systems. The technologies and future trends outlined above aim to improve clinical outcomes, enhance patient safety, and reduce healthcare costs. Further clinical research, based on promising preclinical advancements, is essential to achieving these goals. Collaboration among physicians, materials scientists, engineers, and biotechnologists will be crucial for the continued success and implementation of these innovations in implantable prosthetics.

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5 Additive Manufacturing in 3D Printed Scaffolds for Tissue Engineering Applications

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5.1 INTRODUCTION

Traditional manufacturing methods involve either formative processes, such as using molds, or subtractive processes, such as machining. These methods need several phases and expensive infrastructure, which hinders the capacity to make fast alterations to the final product [1]. 3D printing, also known as additive manufacturing (AM), has become a reliable method for creating intricate products with complicated shapes in a cost-efficient and timely manner over the last 40 years [1–3]. The fundamental principle of 3D printing, which emerged in the 1980s, is the process of adding material layer by layer in a 3D space, following instructions from a computer-generated model [4]. Conventional manufacturing processes are limited in their ability to manufacture intricate designs, making them challenging or even unfeasible. However, the advent of advanced manufacturing techniques has enabled the development of highly complex designs, leading to increased usage across multiple industries [1]. The utilization of 3D printing is playing an increasingly essential role in healthcare, particularly in tissue engineering (TE) [5–7], surgical planning [8], therapeutic delivery [9–11], and implant design [12], and bioprinting is an emerging and fast-growing application of AM. It enables the precise placement of cells in a three-dimensional (3D) environment [13]. This allows for the creation of in vitro models for medicine testing and illness simulation, as well as the manufacturing of implantable tissues like bone [14], cartilage [15], or skin [16].

TE is the utilization of clinical, organic, technical, and biochemical principles to restore and renew live tissue by employing cells, biomaterials, and biological agents [17]. The limited availability of organs for transplantation, the occurrence of organ infections, the prolonged recovery time, and the risk of rejection are the primary drivers behind the progress of TE in the field of replacing and repairing damaged tissue. When creating a TE construct, it is vital to take into account three fundamental elements: cellular regeneration, growth factors, and scaffolds. Currently, there has been significant research into the manufacture of TE scaffolds utilizing various AM techniques. This is because these scaffolds offer exceptional mechanical

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support, improved cell adherence, and greater cell proliferation in areas with defects. Moreover, these approaches have the aptitude to create permeable and complex constructions. Moreover, AM methods have the capacity to build structures in an eco-friendly and sustainable way, hence reducing the amount of waste produced from the materials used [18].

Biodegradable and biocompatible materials are essential for creating an optimal scaffold because they have the capability to interact with the biological components of the human body. The scaffold was commonly fabricated utilizing a range of materials, including polymers, ceramics, metals, and composites. Researchers in recent decades have developed several techniques and approaches, such as electrospinning, biomimetic hydrogels, coatings, and electroactive nanofibrous materials, to enhance the strength of different natural and manufactured substances. The objective is to develop suitable biological frameworks for the formation of functional tissues and organs within live organisms. Afterward, the transplanted cell will replace the scaffold once the damaged cells have adequately regenerated. As a result, there is currently a significant amount of research being conducted on materials that can generate organic tissues for TE scaffolds [19–24].

In 2017, Jafari et al. [25] did a study on scaffold materials obtained from natural sources: synthetic polymers. An assessment was carried out to examine the influence of the structural and chemical characteristics, including pore size, scaffolds, architecture, and microstructure. The work demonstrates that changes in pore sizes have a substantial influence on cell growth. In 2018, Yang et al. [26] did a study on the development of printable polymers that are compatible with living organisms. These polymers are made from materials derived from living sources and are created using techniques of 3D printing. The review examined three main AM techniques used to make intricate scaffold constructions: fused deposition modeling (FDM), inkjet, and stereolithography (SLA) [27]. The potential of soy protein and soybean oil in the construction of scaffolds was also assessed. Furthermore, Jammalamadaka et al. [28] and Roseti et al. [29] investigated the utilization of ceramic, polymer, and composite biomaterials for constructing scaffolds by 3D printing methods. Jammalamadaka et al. [28] examined two main factors: biomaterial and scaffold construction techniques. However, Roseti et al. [29] performed a thorough examination of the methods employed in the creation of scaffolds for bone TE. Both assessments examined the challenges faced and highlighted the significance of actively fostering fresh perspectives and finding future paths for incorporating manufacturing in TE applications.

Figure 5.1 provides a concise overview of the comparisons between the strategies and summary of functional AM in 3D printed scaffolds for TE.

5.2 APPLICATIONS OF ADDITIVE MANUFACTURE IN TISSUE ENGINEERING

According to a recent analysis by Wohlers [31], the AM market is projected to expand to $21 billion by 2020 from $6.1 billion in 2016. Presently, the biomedical industry comprises 11% of the total AM market. It is expected to play a significant role in

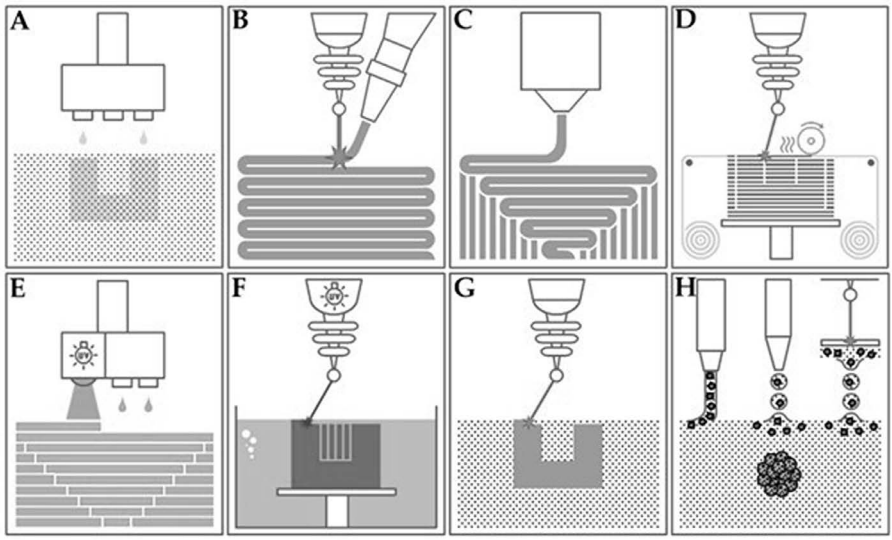

FIGURE 5.1 Classification of additive manufacturing techniques. (A) Binder jetting is a process that involves spraying a liquid binder onto a specific area of powdered material and subsequently adding more powder. The series is cyclical. (B) The process of using a laser to melt metal and expel it through a nozzle is referred to as directed energy deposition. (C) Molten thermoplastics are forced through a nozzle and quickly cooled on the print bed. (D) Sheet lamination entails the precise cutting of a material sheet using either a precision blade or laser. Once the adhesive-coated sheet is attached, the layers are bonded together using heat before the second layer is cut into the desired shape. (E) Material jetting (MJ) involves the process of spraying a layer of liquid resin and then curing it with UV light before proceeding to the next layer. (F) Stereolithography gradually lowers the printing platform into a bath of liquid resin. Ultraviolet light causes the resin to harden. The print bed moves incrementally, adding one resin layer at a time. (G) The print bed in powder bed fusion is uniformly covered with metal powder. Laser melting is a process that transforms powder into a solid layer. Once the print bed descends, a fresh layer of powder is added to the previous layer, and this sequence is repeated. (H) In extrusion bioprinting, a nozzle or needle is used to dispense a bio-ink, which is a combination of cells and a carrier substance. The bio-ink undergoes crosslinking or curing to form distinct layers. Inkjet bioprinting utilizes picolitre-sized bio-ink droplets to create fibers on a print bed. Laser-assisted bioprinting employs a laser pulse to expel bio-ink droplets from a surface and manipulate their form [30].

driving the advancement and expansion of AM technology (Figure 5.2). Biomedical applications possess distinct requirements:

The level of intricacy is high: The complexity and innovative methods present difficulties for biomedical research. AM has the potential to facilitate the expansion of innovative biomedical implants, accurate medicine delivery systems, and customized tissues and organs [32]. AM's versatility allows for the creation of complicated shapes using advanced materials such as semi-crystalline polymeric composites [33].

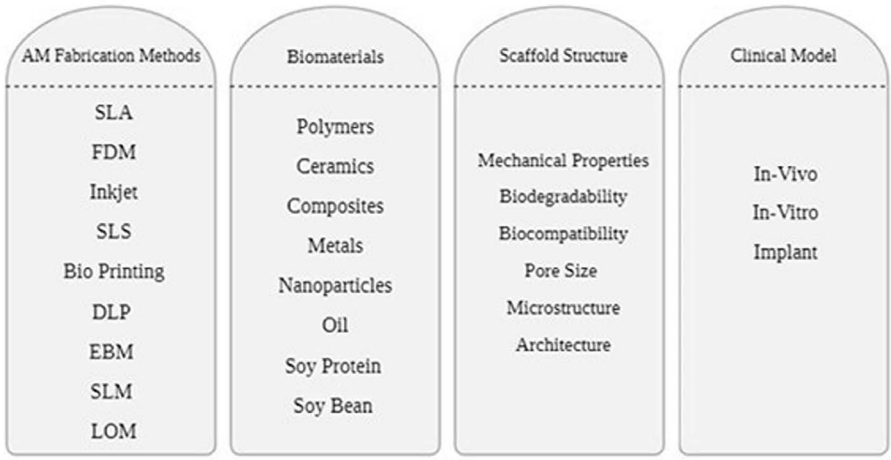

FIGURE 5.2 Summary of functional additive manufacturing in tissue engineering (3D printed scaffolds).

Created by the authors according to References [25, 26, 28, 29].

Personalization and individualized requirements of patients. Biomedical applications necessitate customization according to the individual patient, encompassing implants and medicine dosage. AM holds significant promise for the development of personalized biomedical goods, encompassing a wide range of devices, including hearing aids, biomedical implants, customized orthotics, and prostheses [34, 35]. AM enhances the efficiency and effectiveness of surgical planning while also minimizing the necessity for further procedures to personalize the implant. AM will also tailor medicine dosages and release patterns according to individual needs [11, 36].

Limited Manufacture Quantity

AM is a more economically efficient option as likened to conventional industrial techniques for smaller manufacture quantities, which are commonly found in the biomedical sector. Furthermore, it enables the production of intricate items without the need to create new tooling fixtures for each manufacturing process. AM has the ability to create prototypes of parts more quickly than traditional manufacturing techniques like molding, forging, and milling, completing the process in a significantly shorter period of time [37].

5.3 CONVENIENT PUBLIC ACCESSIBILITY

Researchers can easily share AM CAD data to reproduce the exact design. The National Institutes of Health (NIH) has established the initiative 3D Print Exchange, which allows for the free sharing of AM files.

Bio-fabrication involves the production of organs and tissues by methods such as bio-assembly, bioprinting, and maturation [21]. Bio-fabrication is distinct from AM

due to the incorporation of cells into biomaterials to create bio-inks [38]. Bioprinting, which involves the use of bio-inks, is integrated with robotic dispensing, inkjet printing, and laser-induced forward transfer (LiFT) [21]. The literature extensively covers these specialized procedures [39]. Biomaterials, biomolecules, and cells are integrated and cultivated to form specific shapes and tissues. Biomaterials provide structural support and physical cues, while biomolecules direct tissue regeneration. Various bio-inks and cells are combined to fabricate intricate tissues and organs. Advanced imaging techniques enable precise measurement of the composition, shape, and size of imperfect components. The use of autologous cells from the patient minimizes the risk of organ or tissue rejection. Both in vitro and in vivo experiments have been conducted to generate cartilage [40], bone [41], branched vascular trees, aortic valves [39], and absorbable tracheal splints [42]. An essential objective of bio-fabrication is to generate tissues within the body to directly repair organs and tissues. This has already been successfully accomplished to some extent with skin, bone, and cartilage. Bio-invented components will also serve as prototypes for poisonousness assessments, illness mockups [43], and for evaluating adverse responses to medications, including in a specific way for the patient [44].

The present bioprinting techniques are limited due to the necessity of handling delicate cells. For instance, with micro-extrusion bioprinters, it is crucial to maintain a low pressure while expelling the bio-ink to prevent any distortion of cellular structures and potential cell damage. Extrusion pressures at high levels can result in a decrease of up to 40% in the number of cells that can be used. Inkjet bioprinting employs elevated temperatures throughout the manufacturing process, reaching up to 300°C within the nozzle. However, the cells remain unharmed as the heating is localized and lasts for a few ~2 μs. Moreover, it only raises the local temperature by a modest range of 4°C–10°C [45, 46]. An even more pressing concern revolves around the selection of bio-ink scaffolds. Specifically, it is necessary for cells to remain adhered to the scaffolds and provide sufficient protection against mechanical and thermal stresses simultaneously. In addition, it is necessary for them to stimulate the required cellular growth and reproduction while avoiding the formation of undesired cell types [47]. The chosen material must exhibit cytocompatibility to ensure that it does not elicit immunological and inflammatory reactions, as well as premature stem cell differentiation [48]. Several bio-ink scaffolds have been created to tackle the aforementioned problems; however, there are still constraints in achieving the best possible 3D printing of biomaterials [49]. An important and difficult task in the field of bio-fabrication is the creation of organs with blood vessels [21]. In order to sustain the metabolic processes of huge organs, it is imperative to devise techniques for constructing intricate circulatory innervation and systems. Zhang et al. [50] conducted a comprehensive analysis of the latest advancements in the field of 3D bioprinting of blood vessels and the creation of useful vascularized organ. There are currently two main obstacles to printing high-resolution tiny tissues: the absence of suitable mechanical characteristics for vascularized tissues and the need for further research and development in this field. Overcoming these challenges is necessary to successfully create 3D printed tissues. Recent advancements in bio-ink technology have demonstrated the possibility of AM in TE for intricate human organs. Researchers are investigating the use of bioreactors in conjunction with substances that stimulate

the growth of blood vessels and nerves to develop fully formed bioprinted components with the required properties. The utilization of various bio-inks and AM techniques is yielding promising outcomes in the fabrication of tissue constructs at a human-scale [51, 52]. In situ bioprinting, a cutting-edge approach, has the potential to transform the biomedical field by enabling tissue regeneration.

The pharmaceutical business will greatly benefit from AM. Hence, there will be a significant transformation in the processes of drug production and distribution. The initial AM medication was granted approval by the Food and Medication Administration (FDA) in 2015 [11].

Researchers are now developing many advanced drug delivery systems [53], including solid dosage forms (which are the most extensively investigated due to their ease of commercialization) [54], topical drug delivery systems [55], and implantable drug delivery vehicles [56]. AM has the ability to manipulate the release profile of medications by modifying the 3D shape [54], microarchitecture of drug delivery systems, and location of active agents [57]. AM has developed microcapsules, nanosuspensions, synthetic extracellular matrices, antimicrobial micropatterns, mesoporous bioactive glass scaffolds, and multilayer drug delivery systems [58].

The future will enable the production of customized medications as needed, tailored to specific dosages and individual pharmacogenetic characteristics. Variables for example race, age, or gender could be utilized to create the greatest optimal medication [58]. It is possible to consolidate multiple medications into a single tablet, while ensuring that each drug is released in a regulated manner. Another use that can be done on-demand is the additive production of unstable medications that have a limited shelf-life [11]. Various active components, including steroidal anti-inflammatory medications, acetaminophen, theophylline, caffeine, and others, have been examined [58]. Computational models can be used to forecast the release pattern of drug delivery systems using AM. It is necessary to study the impact of factors such as geometric design, microarchitecture, arrangement of passive and active agents, and their release methods.

5.4 CHARACTERISTICS OF TISSUE ENGINEERING SCAFFOLDS

Scaffolds designed for cell migration to soft tissue or bone injuries have distinct biological and physical characteristics. Production should utilize both in vitro and in vivo physiological settings [59]. Additionally, the extracellular matrix (ECM) is essential in promoting cell proliferation, development, and adherence inside the scaffold [60]. The ECM is essential in TE by virtue of its intricate protein network, which constructs and sustains the cellular microenvironment. Additionally, it offers 3D mechanical support and biochemical cues to the surrounding cells, influencing several aspects of cell behavior such as shape, proliferation, migration, and differentiation [61].

5.4.1 Biodegradability

Scaffolding is used to give temporary support for damaged areas of the body's structure, allowing for the transfer of stress and gradual degradation to take place. The

degradation of the scaffold is necessary for cells to synthesize their own ECM, making it unsuitable for use as a permanent implant [62]. The rate at which constructed scaffolds degrade should be comparable to the rate at which human tissue forms in the body [63]. For instance, bioresorbable materials and non-toxic substances will undergo degradation over time or as a result of metabolic processes within the body [59]. Biodegradable polymers are extensively utilized because of their flexible mechanical qualities and ability to decay, unlike metallic implants. Metallic scaffolds require a second procedure to remove them as they cannot naturally degrade within the human body.

5.4.2 Biomimicry

Scaffolds must be designed to create structures that closely resemble the tissues or organs they are intended to replace. These structures should possess optimal mechanical strength to work effectively from the moment of implantation until the remodeling process is complete. The scaffold must precisely mimic the composition, structure, and function of the tissue it is replacing in order to effectively transfer the load and totally replace the newly produced tissue after degradation [64]. The selection of composition for scaffold fabrication, such as biomaterials, should be based on the specific properties required for constructing different types of tissues, such as orthopedic implants [65, 66], organs [67, 68], or skin [69], each of which has distinct structural needs. The scaffold's structure, including its porosity and internal architecture, must facilitate nutrition transfer upon implantation. Once degradation occurs in the scaffold, the mechanical qualities will gradually diminish. This is because the porosity of the scaffold has a significant impact on its mechanical properties. For certain individuals, the healing process is faster and fractures typically reach a point where weight can be put on them in approximately six weeks. However, the healing process takes longer for senior individuals [62]. Hence, it is crucial to prioritize these factors in order to create and develop an optimal framework.

5.4.3 Porosity

A substantial number of cells need to be cultivated within the scaffold in order to reinstate the functionality of the tissue or organ. The porosity of the scaffold is crucial for cell development and the supply of nutrients. An optimal scaffold possesses a combination of large pore sizes and high porosity to facilitate cell movement, as well as small hole sizes to increase surface area and reduce ligand density for binding multiple cells. The scaffold utilized in TE must possess a pore size ranging from 50 to 900 μm and a minimum porosity of 70%. The optimal scaffold porosity is contingent upon the specific type of cell or tissue being produced [62, 70].

5.4.4 Biocompatibility

The primary consideration in scaffold creation for TE is biocompatibility, as scaffolds are foreign materials that have the potential to induce rejection and damage [22]. Scaffold biomaterials should not induce inflammation, immunogenicity, or cytotoxicity in organs, tissues, or native cells [59]. Biocompatibility encompasses dynamic

and controlled factors that influence the interaction between tissues and the immune system. Additionally, it enhances cellular activity in biological and functional human tissues, rendering it indispensable for transplantation and proper functioning [21]. Biocompatible material development has significantly advanced in the past decade to fulfill the requirements of TE scaffold implantation and tissue regeneration.

5.5 INDUSTRIAL PRODUCTION METHODS AND TECHNIQUES

Historically, the predominant techniques for scaffold manufacturing have been gas forming [71, 72], electrospinning [73], injection molding [70], and freeze-drying [74]. At present, AM techniques are extensively utilized in TE since they have the capability to develop intricate scaffold architectures. The manufacturing of scaffolds should be economically efficient and capable of being scaled up, rather than being produced in tiny batches in a research facility. Adhering to manufacturing standards is crucial to guarantee that the TE construct, which has been validated through clinical and scaffold testing, undergoes both in vitro and in vivo assessments prior to proceeding with actual human implantation [62].

5.6 BIOMATERIALS USED IN TISSUE ENGINEERING

As previously said, material is crucial in TE for facilitating cell proliferation [75], differentiation [76, 77], and cell regeneration [78, 79] due to its distinct material qualities [80, 81]. TE scaffolds require biodegradability, biocompatibility, mechanical strength, and a porous structure to facilitate the interchange of cell nutrients. Stainless steel plates are utilized for bone internal fixation upon implantation. Research has been conducted on biocompatible metals, for example, titanium alloy and magnesium, which are not impacted by non-biocompatible substances, in order to enhance surface compatibility. In 1974, the first polymer biological scaffold was created by combining collagen and chondroitin 6-sulfate to form a composite material. The guinea pigs were administered this scaffold [82]. Since the early 1900s, polymer materials have been utilized in implantation procedures. In 1969, Hench made the discovery that ceramic materials have the ability to form a link with living bones [83]. Although TE was initiated in the early 1970s, the phrase "tissue engineering" was not coined until 1987 [84]. Subsequently, there has been significant progress in the advancement of nanoparticle technology and the creation of composite scaffolds in TE. AM technology utilizes several materials for scaffold fabrication, including metals, ceramics, polymers, composites, and nanomaterials [85–87]. Figure 5.3 shows an overview of the structures designed and printed by a 3D printer using different materials.

A summary of the primary submissions, benefits, and problems associated with the main ingredients used in scaffold manufacturing with additives is shown in Table 5.1.

5.6.1 Polymers

Polymers, like collagen, chitosan, hyaluronic acid, fibrin, and alginate, are obtained from natural sources such as the human body, plants, insects, and animals. The material properties closely resemble those of natural tissue and bone matrix proteins,

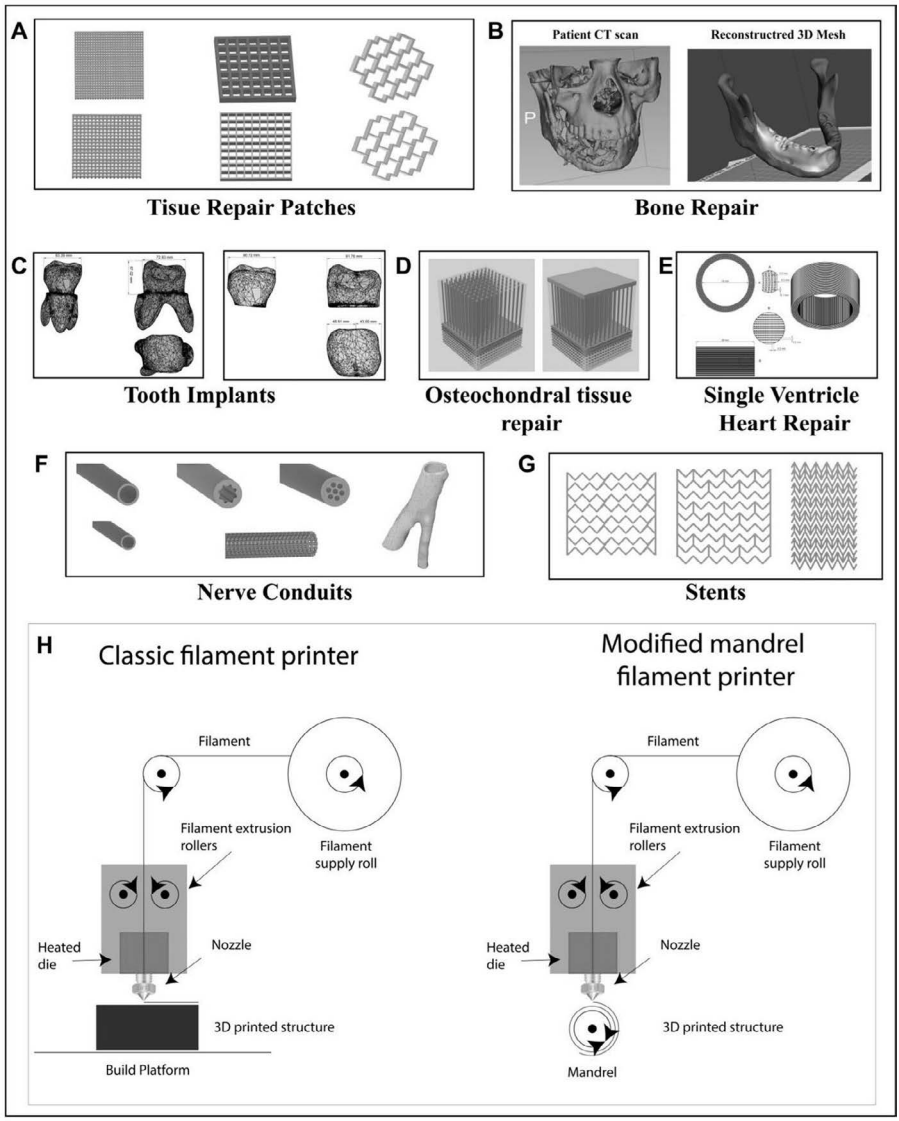

FIGURE 5.3 (A) Tissue regeneration patches for heart tissue repair can be created using grid, woodpile, and accordion configurations. (B) Mandible restoration can be achieved by using CT-derived bone implants. (C) Tooth implants can be created using CT-derived technology. (D) Osteochondral tissue repair plugs are available for repairing damaged tissue. (E) A permeable mesh design can be used for repairing a single ventricle heart. (F) Nerve guiding conduits, including a CT scan mesh that maps a human sciatic nerve, can effectively repair complex nerve junctions. (G) Assortment of polymer stents that have been flattened. (H) Diagram comparing the filament extrusion procedures in a regular filament printer (left) with our customized mandrel printing method (right) [88].

TABLE 5.1
Summarization of the Primary Applications, Aids, and Problems Associated with the Main Ingredients Used in Scaffold Industrial with Additives

Biomaterial	Application	Benefits	Challenges
Composite and polymer	Biomedical	Mass-customization Fast prototyping Complex structures Cost-effective	Limited number of polymers to choose from Poor mechanical properties
Metal	Biomedical	Reducing material waste Multipurpose optimization Fewer assembly components High number of customizations Repair and restoration of worn and damaged parts	Limited selection of alloys machining, chemical etching, or heat treatment
Ceramics	Biomedical	Controlling porosity of lattices Microstructures and compositions are controllable Reduced fabrication time Various scaffolds and structures are printable for the body	A limited number of ceramics can be printed with a 3D printer

such as collagen and osteopontin, which have the potential to enhance cell proliferation and differentiation. Commonly utilized were synthetic polymers, including poly-L-lactide (PLLA), PCL, and PLA, as well as copolymers such as PLGA and polyglycolic acid (PGA). Synthetic polymers are human-made polymers that exhibit greater flexibility and durability. By altering their chemical composition, these materials can be readily molded and resized to enhance their mechanical properties and material characteristics [59, 62, 63, 89–91].

In another study as shown in Figure 5.4, the creation of intricate frameworks made up of micro- and nano-structures is a crucial objective in TE. The integration of sequential 3D printing and electrospinning allows for the construction of these

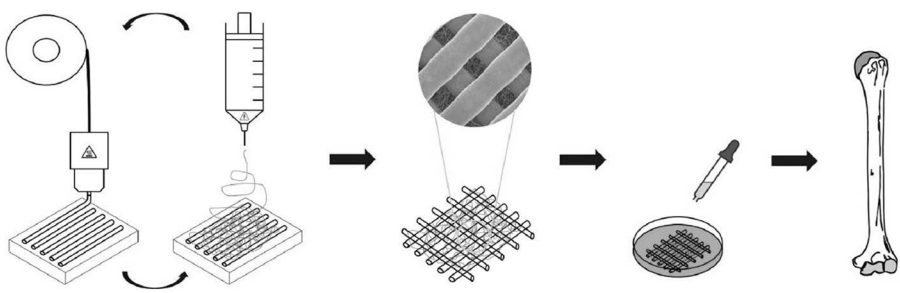

FIGURE 5.4 These scaffolds were made from polycaprolactone (PCL) and consisted of multiple layers of mesh [92].

multi-scale structures. The study successfully fabricated dual scaffolds using a combination of 3D printing and electrospinning techniques. The optical and scanning electron microscopy techniques were used to evaluate the macro- and micro-porosity of the scaffold. The results revealed that the electrospun fibers created aligned meshes within the scaffold's pores. As a result, the scaffold became more hydrophilic over time, which improved the ability of cells to stick to it and develop. In addition, compression tests conducted in alternating cycles revealed a favorable ability of the scaffolds to regain their original shape [92]. Also, in Figure 5.5, you can see some texture repair patches that were designed with CAD and printed with a 3D printer.

5.6.2 Composite

Composite materials, as described by Chaikof [93], consist of two or more chemical components that possess unique material qualities necessary for replicating the biological characteristics of specific tissues. Prior researchers have mostly focused on investigating composites consisting of polymers and ceramics in the field of TE. The reason for this is that ceramics possess comparable properties to human bones; however, polymers can enhance the fragility of ceramics and strengthen the bond between the bone and the surrounding matrix. Lately, there has been extensive observation of the amalgamation of nanoparticles, mostly because of their nano-scaled structure, which has the potential to increase the material composition when integrated with other types of materials. Materials containing nano-sized features exhibit behavior that closely resembles the cellular microenvironment and have the ability to govern cell behavior. This is because the ECM of human tissue is often composed of nanocomposites. Nanocomposites play a crucial role in bone TE and dentistry due to their ability to enhance cell ingrowth. Studies have shown that a composite scaffold consisting of nano-scale and microscale components exhibits enhanced biocompatibility and promotes cell development [94–97].

5.6.3 Metal

The process of implantation commenced by utilizing stainless steel bone anchoring plates. Metallic implants have existed since the early 18th century; however, metals are nonbiodegradable and might potentially induce side effects such as metal allergies. Over the years, scientists have applied coatings and made alterations to biocompatible metals in order to enhance their compatibility with biological systems at the surface level. The study investigated the use of titanium, titanium alloy, magnesium, and silver in thermoelectric (TE) applications. Studies indicate that magnesium alloys possess biocompatibility, biodegradability, and are well-suited for use in orthopedic implants. Furthermore, this obviates the necessity for surgical removal of steel scaffolds. The researcher evaluated the potential of magnesium as a TE material using the available data. Titanium (Ti-6Al-4V) covered with alumina and nickel-titanium alloys (NiTi) has been researched and employed in the field of orthopedic due to its robustness and compatibility with the human body. Nevertheless, there are certain difficulties encountered with the process of metallic implantation. As previously stated, magnesium exhibited favorable degrading performance. However, this

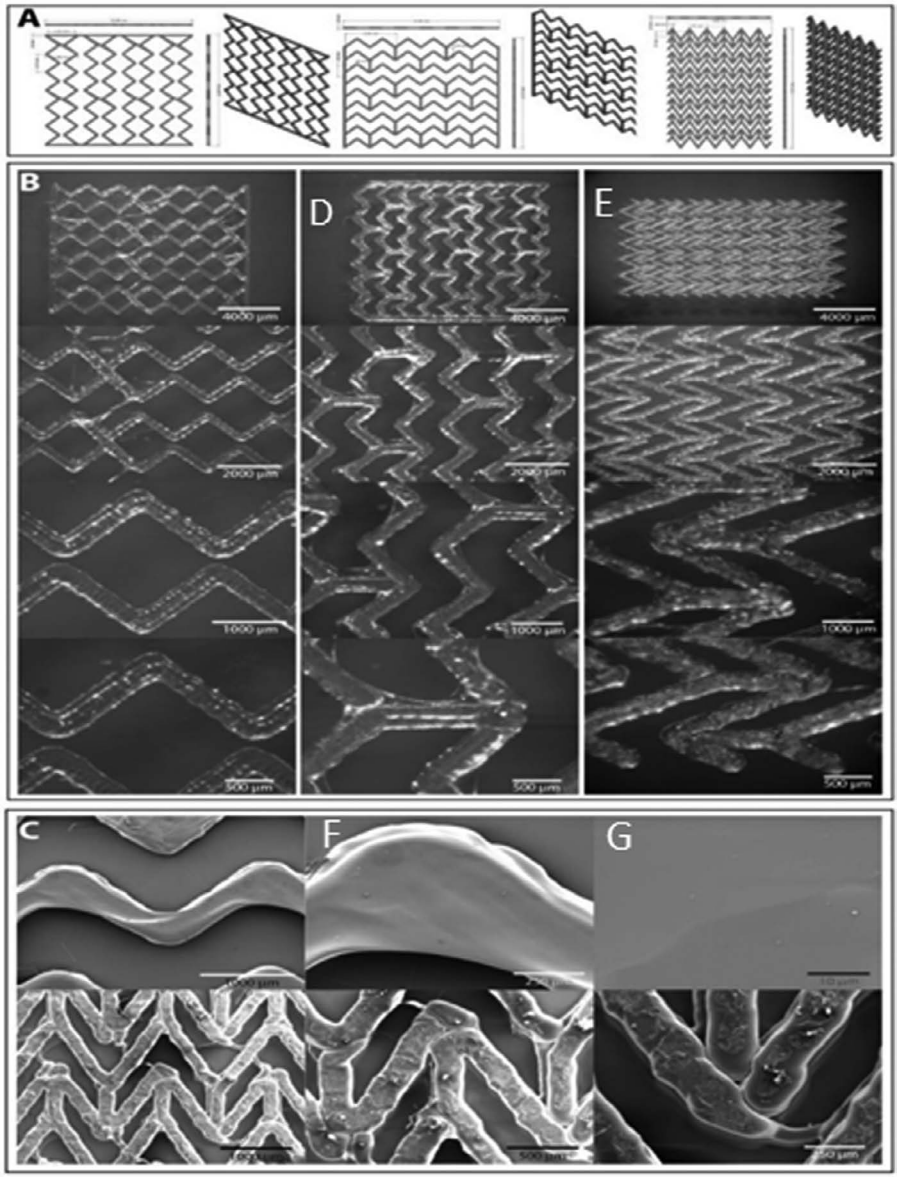

FIGURE 5.5 CAD designs depicting various tissue repair patches are presented in the following formats: (A) a woodpile configuration characterized by a strut diameter and pore size of 0.4 mm each, (B) a woodpile arrangement featuring a 0.4 mm strut diameter and 0.8 mm pore size, (C) a grid pattern with struts measuring 0.2 mm in diameter and pores spanning 2 mm, (D) an accordion design with 0.4 mm strut diameter and pores created by the overlap of two squares, each 2 mm in diameter. Additionally, (E) a four-layer woodpile structure with a 0.4 mm nozzle, printing at a speed of 2 mm/s, and 0.4 mm gaps, (F) a similar woodpile structure but with 0.8 mm gaps, and (G) photographic and SEM images illustrating the grid design with 0.2 mm struts manufactured using a 0.2 mm nozzle at a print speed of 2 mm/s [88].

may lead to a decline in mechanical performance prior to complete tissue restoration. On the other hand, the prolonged existence of metals like titanium and steel in living organisms will heighten the likelihood of infection. Consequently, scientists are currently examining more effective approaches and recommendations, such as using nanoparticles, to enhance metallic implants and overcome challenges [98–101].

5.6.4 Ceramics

Ceramics, similar to polymers, can be either naturally occurring or artificially produced. The exceptional mechanical qualities, low elasticity, and rigid, fragile surface of ceramics make them optimal materials for scaffolding. These characteristics imitate the natural composition of bones, hence enhancing the growth of osteoblasts. Ceramics are frequently employed in dentistry and orthopedic surgical procedures. Common synthetic ceramic materials include beta-tricalcium phosphate/bioactive glass (β-TCP/BG), tricalcium phosphate (TCP), hydroxyapatite (HA), magnesium-doped calcium silicate (CaSiO3), beta-tricalcium phosphate (β-TCP with Mg), and calcium phosphate cement (CPC). Human bones and teeth are naturally formed ceramics that are made through the gradual accumulation of atoms at ambient temperature. Ceramics, commonly employed in bone TE, exhibit excellent resistance to deformation. Nevertheless, ceramics possess limitations that can impact the functionality of scaffolds. These limitations encompass the tendency to be brittle throughout the manufacturing process, a slow rate of decomposition, and a lower level of flexibility compared to polymers [102–104].

5.6.5 Nanomaterials

Researchers have enhanced the properties of nanomaterials by augmenting their surface area, nano-roughness, and surface chemistry. This has led to improved control over the behavior of stem cells. In addition, nHA, a nanomaterial that has similar inorganic components with bone matrix, is currently being extensively utilized in composite materials. The utilization of nano-scale particles in TE is on the rise, primarily because they possess inherent properties that closely resemble those found in biological settings. This enables them to effectively restore and improve the physiological function of living tissues or organs. In addition, nanomaterials are anticipated to have a significant impact on TE applications, contributing to the successful implementation of nanotechnology in future developments [95, 105–107].

5.7 CONCLUSION

AM, commonly known as 3D printing, has revolutionized various industries, including the field of TE. 3D printed scaffolds have revolutionized TE and personalized treatment in regenerative medicine. These scaffolds serve as a platform for cell growth and tissue regeneration, offering a promising solution to repair and replace damaged or diseased tissues in the human body. One of the key advantages of using 3D printed scaffolds in TE is the ability to create complex structures with precise control over their architecture and properties. Traditional manufacturing methods

often struggle to produce intricate designs required for mimicking the complexity of native tissues. With 3D printing, researchers can fabricate scaffolds with customizable shapes, porous structures, and mechanical properties tailored to specific tissue types. This level of customization enables the creation of patient-specific implants that can enhance integration with the host tissue and promote better healing outcomes. Moreover, it is possible to fabricate scaffolds that closely resemble the ECM present in the body by utilizing 3D printing technology and biocompatible materials. The ECM is essential for tissue regeneration as it plays a crucial role in cell adhesion, proliferation, and differentiation. 3D printed scaffolds can create a conducive environment for cell growth and organization into functional tissues by mimicking the properties of the ECM. Researchers have explored several biomaterials, such as synthetic polymers like poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), as well as natural polymers like collagen and gelatin, in order to develop scaffolds that promote cell adhesion and tissue formation. In addition to material selection, the design of 3D printed scaffolds plays a critical role in determining their performance in TE applications. Researchers have employed computer-aided design (CAD) software to create intricate scaffold geometries that mimic the hierarchical structure of native tissues. By optimizing pore size, shape, and interconnectivity, researchers can regulate nutrient diffusion, waste removal, and cell infiltration within the scaffold. Moreover, the incorporation of bioactive molecules, growth factors, and drugs into the scaffold design can further enhance tissue regeneration and modulate cellular behavior for specific therapeutic outcomes. The versatility of 3D printing technology allows researchers to explore various fabrication techniques, including SLA, FDM, selective laser sintering, and inkjet bioprinting, to create scaffolds with different properties and functionalities. Each of these techniques offers unique advantages in terms of resolution, speed, scalability, and material compatibility, enabling researchers to choose the most suitable method based on the desired scaffold characteristics and application requirements. For instance, bioprinting techniques have gained attention for their ability to deposit multiple cell types and biomaterials in a precise spatial arrangement, mimicking the complex organization of native tissues. In addition, the utilization of 3D printing and advanced imaging methods such as MRI and CT have enabled the development of customized scaffolds for personalized TE purposes. Medical imaging data can be utilized by researchers to create digital models of the patient's anatomy. These models can then be used to develop scaffolds that accurately match the form and size of the defect site, hence enhancing the fit and function of the implant. Patients derive advantages from this personalized approach, as it enhances the compatibility of the scaffold with the body and strengthens its structural integrity, while reducing the risk of immunological rejection and implant failure. Despite the significant progress in 3D printed scaffolds for TE, several challenges remain to be addressed to translate these technologies into clinical practice. One of the primary concerns is the need to optimize the mechanical properties and degradation kinetics of scaffolds to match the target tissue requirements. Balancing the scaffold's strength, flexibility, and degradation rate is crucial to ensure long-term stability and functionality in vivo. Additionally, improving vascularization within the scaffold to support nutrient transport and waste removal remains a critical challenge for the successful integration of

engineered tissues with the host vasculature. Furthermore, the regulatory approval process for 3D printed scaffolds in TE applications poses a significant hurdle due to the complex nature of these medical devices. Ensuring the quality, safety, and efficacy of 3D printed scaffolds requires rigorous testing and validation to meet the regulatory standards set by health authorities. Collaborations between clinicians, industry partners, researchers, and regulatory agencies are essential to navigate the regulatory pathway and bring 3D printed scaffolds from the laboratory to the clinic. In conclusion, AM in 3D printed scaffolds for TE applications holds great promise for advancing regenerative medicine and personalized healthcare. The ability to create patient-specific implants with tailored properties and functionalities opens up new avenues for treating various medical conditions, including bone defects, cartilage injuries, and organ failure. Using the capabilities of technology of 3D printing, researchers can continue to innovate and optimize scaffold design, material selection, and fabrication techniques to overcome existing challenges and realize the full potential of TE in improving patient outcomes. With ongoing advancements in biomaterial science, bio-fabrication technologies, and translational research, 3D printed scaffolds are poised to transform the landscape of regenerative medicine and shape the future of healthcare.

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6 Mechanical and Tribological Properties of Polymethylmethacrylate-Based Dental Biocomposites

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6.1 POLYMETHYLMETHACRYLATE/OTHER ORGANIC POLYMERS COMPLEX

6.1.1 Introduction

Polymethylmethacrylate (PMMA), belonging to the synthetic resin polymers, is polymerized from methyl methacrylate (MMA) monomers. It was first synthesized in 1902 and commercialized in the 1930s. The structures of MMA and PMMA are depicted in Figure 6.1.

In the field of dentistry, PMMA is commonly used for fabricating denture bases, orthodontic retainers, temporary restorations, and artificial teeth, etc. PMMA falls into four categories based on its curing methods: thermal-curing, microwave-curing, cold-curing, and light-curing. Excellent mechanical properties are needed for PMMA-based denture materials as they are subjected to complex masticatory forces in the oral cavity over a long period. The basic physical properties of PMMA are shown in Table 6.1.

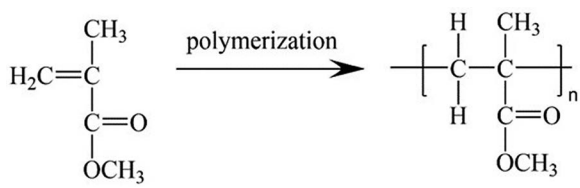

FIGURE 6.1 Chemical structures of MMA and PMMA.

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TABLE 6.1
Basic Physical Properties of PMMA

Property	PMMA Performances
Color	Transparent
Density at room temperature (g/cm^3)	1.17–1.19
Glass transition temperature (°C)	120
Linear thermal expansion (×10^{-5} mm/mm.K)	6.3
Thermal conductivity (°C/cm)	5.7×10^{-4}
Solubility (mg/cm^2)	0.02 (water)
Rockwell hardness	M90–M100
Young's modulus (MPa)	2000–3000
Elastic modulus (GPa)	2.6
Tensile strength (MPa)	48–62
Impact strength (J)	0.98–1.27

Ideally, denture bases should possess high flexural strength to withstand the complex forces of mastication without getting permanent deformation or fracture. Meanwhile, fracture toughness and impact strength are also crucial for denture base application. Fracture toughness describes a material's resistance to crack propagation caused by surface flaws or defects, while impact strength describes the energy required to cause fracture. High-impact strength can prevent dentures from fracture under high-impact forces (e.g. accidental drops). The impact strength of denture bases can significantly decrease due to the presence of tiny surface defects caused by abrasion; even microscopic surface defects can lead to crack propagation and fracture; thus wear resistance also needs to be considered. Although PMMA has been widely used in various dental applications, the drawbacks of the material prevent it from achieving the desired performance for denture bases or other dental applications. For example, its polymerization shrinkage (linear and volumetric shrinkage) may lead to significant dimensional changes and inaccuracy; unsatisfactory flexural strength and impact strength make dentures prone to fatigue failure or accidental fracture, weak bonding strength, low thermal conductivity, susceptibility to cracking, high thermal expansion coefficient, residual monomers, etc. Improving the performance of PMMA has become a focus of the current research.

Developing composite materials of PMMA with other organic polymers is an effective solution. Composite materials refer to new materials formed by combining two or more different components, and the properties of these new materials can be customized by adjusting the morphology, content, and addition form of each component. This section will discuss the improvement of PMMA/other organic polymer complex materials in mechanical properties and other characteristics synthesized through various processes, including PMMA/organic polymer blends, PMMA/organic polymer interpenetrating networks, organic polymer fiber-reinforced PMMA complex, and PMMA/organic polymer electrospinning.

6.1.2 PMMA/Organic Polymer Blends

Polymer blending is widely used for enhancing the properties of the polymeric complex materials. Polymer blends have emerged as a cost-effective alternative to developing new monomers and polymers, saving on research and development costs and reducing the cost of large-scale production and commercialization. The performance of polymer blends depends on their blend miscibility. Miscible blends can obtain the advantages of each polymer and improve the performance of the polymer blend, while immiscible blends result in poor performance [1, 2]. The most common blending method is melt-blending, such as internal mixing in extruders, hot roll blending, and internal mixing in mixing machines. The uniformity of the product is related to mechanical efficiency. Twin-screw extruders are beneficial as they provide powerful shear forces while enabling continuous production [3]. Solution blending is theoretically feasible but is not industrially viable due to solvent recovery issues and low efficiency. Emulsion blending, which produces homogeneous blend resins, is only suitable for certain varieties produced by the emulsion method.

Polyimide (PI) is a high-performance polymer with excellent mechanical, thermal, and chemical stability. It is often used to modify other polymeric materials to enhance their thermal stability or mechanical performance. Researchers have achieved the most ideal enhancement of PMMA resin matrix by blending PI with PMMA at a ratio of 0.6%, resulting in a 13.5% increase in flexural strength [4]. The reinforcement effect remained significant even after thermal cycling due to the uniform dispersion of PI particles in the PMMA matrix. The interface between PI particles and the PMMA matrix absorbed part of the stress and buffering crack propagation, thereby improving the material's overall flexural strength.

Polylactic acid (PLA) is one of the most popular bio-based and biodegradable polymers, and it has been applied in industrial and medical fields due to its good mechanical properties and biocompatibility. However, its low toughness and bending performance prevent it from being a long-term temporary or permanent repair material. Recently, researchers have studied different proportions of PMMA and PLA blends as sustainable biomaterials for dental applications [5]. PMMA/PLA blends can simultaneously obtain the benefits of both polymers (with no statistical difference in flexural strength compared to pure PMMA and flexural modulus compared to PLA) and significantly reduce the residual MMA monomer, thus becoming more biocompatible. A 50% PMMA blend ratio may be suitable for long-term temporary and permanent dental restorations.

Kanie et al. blended dimethylmethacrylate urethane ester (UDMA) with PMMA, resulting in minimal fragmentation of the blend and no fracture at the testing speed [6]. The elastic strength and modulus of the material were not significantly different from commercially available acrylic resins.

6.1.3 PMMA/Organic Polymer Interpenetrating Networks

Interpenetrating polymer network (IPN) is a polymer network formed by the interpenetration of two or more cross-linked polymers, resulting in a unique spatial topology structure. PMMA-IPN blend system has overcome the brittleness, poor heat resistance, susceptibility to discoloration, and surface scratching of PMMA to some extent [7].

IPN can be classified as sequential, simultaneous, semi, latex, thermoplastic, and nanocomposite. Researchers have improved impact resistance by synthesizing PMMA-rubber semi-IPN: when cracks reached the rubber interface, crack propagation in the PMMA matrix slowed down, allowing the denture to withstand higher impact stress before fracturing and improving fatigue resistance. Additionally, the rubber's elasticity reduced the composite material's elastic modulus, making it more flexible. Therefore, rubber-modified PMMA is suitable for patients with easily dislodged dentures. The performance of PMMA/rubber composite materials is related to the content of added rubber (styrene-butadiene copolymer), with the elastic modulus and tensile strength of the composite material decreasing as the rubber content increases [8].

6.1.4 Organic Polymer Fiber-Reinforced PMMA Complex

The high polymerization shrinkage of PMMA (linear and volume shrinkage) may cause significant dimensional changes during denture fabrication, resulting in the inaccurate denture edge and poor sealing; meanwhile, the limited flexural strength and fatigue strength of PMMA make the denture base prone to fracture during use. Inspired by natural fiber composite materials such as bone and dentin, artificial fiber-reinforced composite (FRC) materials have been developed. FRC materials are composed of matrix and fibers, with the matrix being the main body and the fibers dispersed within it; fibers are incorporated at a high aspect ratio, precise orientation, and good adhesion to the polymer matrix [9]. The development of FRC materials contributes to improving the mechanical properties of PMMA composite materials and enhancing the durability of PMMA composite materials in high-load clinical applications (such as patients with low vertical distance and single-jaw full-mouth dentures). In the early 1960s, researchers developed the first glass fiber-reinforced material for dentistry, and its first application was for PMMA-based denture. Today, FRC is mainly used for direct and indirect restorations in clinical dentistry, while more complex FRC materials need to be fabricated indirectly in the laboratory. FRCs are also suitable for repairing old metal-based FDPs and ceramic veneer restorations, traditional removable and full-mouth dentures, as well as implant-supported dentures [10]. The combination of CAD-CAM and 3D printing technology to manufacture indirect FDPs is the future development trend [11].

Glass fiber is the most widely studied reinforcing fiber; synthetic polymer fibers such as polyamide, polyethylene, and polypropylene, as well as natural fibers, have also been studied for reinforcement of PMMA composite materials. The loading transfer at the fiber/matrix interface and the mechanical properties of the composite material are mainly determined by the fiber aspect ratio, while the orientation, concentration, pre-impregnation, and silane treatment of the matrix also have an effect on the enhancement of mechanical properties. In order to make FRC materials uniformly void-free, the fibers need to undergo impregnation treatment besides wettable process. Since glass fibers, polyethylene fibers, and polypropylene fibers are hydrophobic and have low surface energy, their compatibility with PMMA is poor. Unprocessed fibers become inclusions within PMMA, destroying the uniformity of the matrix and reducing its mechanical properties. Impregnation of fibers can be performed manually, but for polymers with high-viscosity like PMMA, special

pre-impregnation treatment is required: firstly, PMMA is dissolved and added into the space between the fibers to form a porous solid polymer, so that a second impregnation can be carried out in the subsequent denture fabrication. Well-impregnated FRC ensures that each fiber is tightly wrapped around the polymer matrix, effectively addressing the issue of voids caused by the high viscosity of the resin or polymer shrinkage. Prolonged adhesion between the fibers and the polymer matrix can also be achieved by silanization through the formation of covalent bonds.

Polyamide fibers include nylon and aramid fibers. Aramid fibers possess good wettability, flexural strength, flexural modulus, and biocompatibility. PMMA composite materials reinforced with aramid fiber have shown improvement in the mentioned properties, but it should be noted that the hardness of PMMA composite materials decreases with increasing fiber concentration. Furthermore, the yellow color of aramid itself may have a negative effect on the aesthetic effect of denture materials [12]. Nylon fibers have higher resistance to sustained stress and help improve the structural elasticity, fracture resistance, and flexural strength of PMMA [13].

The addition of polyethylene fibers significantly enhances the impact strength of PMMA and further improvements can be achieved through surface treatment of the fibers. Woven polyethylene fiber reinforcement can significantly increase the elastic modulus and toughness of PMMA. However, the processes for etching, preparation, and positioning of woven fibers are considered challenging to implement [14]. Polypropylene fibers also increase the impact strength of PMMA (Table 6.2). Mowade TK et al. achieved the highest impact strength by using plasma-treated polypropylene fibers, which can be used to reinforce acrylic resin and reduce fracturing [15]. Ismaeel IJ et al. incorporated silanized polypropylene

TABLE 6.2
Improvements of PMMA Mechanical Properties by Different Fiber

Undirectional and woven Aramid fibers	Flexural strength	Improved by 216.6% and 145.7%, respectively
	Flexural modulus	Improved by 193.1% and 124.4%, respectively
Nylon6 and 6.6	Transverse strength (MPa) Mean ± SD	92.72 ± 11.36; 83.36 ± 4.25
	Maximum deflection (mm) Mean ± SD	3.60 ± 0.39; 4.10 ± 0.37
	Impact strength (kN) Mean ± SD	0.45 ± 0.15; 0.44 ± 0.13
Plasma-treated polyethylene fibers and polypropylene fibers	Impact strength ($\times 10^2$ J/m) Mean ± SD	9.096 ± 0.3864; 0.229 ± 0.4714
Silanated polypropylene fibers	Impact strength (kJ/m^2) Mean ± SD	23.1549 ± 4.4210
	Tensile strength (MPa) Mean ± SD	57.1286 ± 1.6710
	Wear rate	0.000010 ± 0.000001

fibers into heat-cured PMMA resin, significantly enhancing the transverse strength, tensile strength, and impact strength of PMMA despite a slightly decrease in wear resistance [16].

6.1.5 PMMA/Organic Polymer Electrospinning

Electrospinning technology is a relatively new technique which involves extruding polymer solutions using a high-voltage source to obtain fibers with different physical and mechanical properties [17]. Polyblend electrospinning combines polymers with different characteristics into one reservoir and then electrospins them together to form a fiber mat. To better control the desired fiber morphology, the blend compatibility and charge interactions of the co-spun polymers need to be considered. Researchers have successfully developed antimicrobial and mechanically reinforced nanofiber mats by multicomponent electrospinning silk fibroin (SF), polyethyleneimine (PEI), and PMMA, which increased the elastic modulus by 52% compared to pure PMMA fibers [18]. This nanofiber mat has the potential to be integrated into PMMA-based denture base resin materials to overcome the drawbacks of PMMA, such as fatigue failure, poor bending and fracture resistance, thermal instability, and susceptibility to bacterial growth. Sun et al. prepared core-shell polyacrylonitrile (PAN)-PMMA nanofibers using co-electrospinning, resulting in a 673.4% increase in tensile strength and an 875.3% increase in tensile modulus; composite materials with 1.2 wt% nanofibers showed a 51.6%, 64.3%, and 152% increase in flexural strength, flexural modulus, and work of fracture, respectively [19].

6.2 POLYMETHYLMETHACRYLATE NANOCOMPOSITES WITH METALLIC NANOPARTICLES OR METAL OXIDES

6.2.1 Metallic Nanoparticles

The porous nature and hydrophobicity of PMMA material used as denture bases making it easy for bacteria and fungi to adhere and form biofilms (Figure 6.2). Especially in elderly patients, the presence of biofilms on dentures is associated with oral infections and systemic diseases, such as denture-related stomatitis (DS) caused by *Candida albicans*. It has been reported that 50%–70% of complete denture wearers suffer from DS [20]. However, due to issues such as recurrent infections and difficulties in sustained local medication, there is currently no gold standard treatment for DS. Researchers are currently attempting to enhance the antimicrobial properties of PMMA materials as an alternative treatment method.

The antibacterial effect of metal nanoparticles has long been recognized. They are defined as metal particles with diameter smaller than 100 nm, possessing superior antibacterial capabilities due to their large specific surface area, high charge, and high reactivity. Among them, the most commonly used antibacterial agent is AgNPs, which exhibit high antibacterial activity against both Gram-positive and Gram-negative bacteria, including highly multidrug-resistant strains such as *Staphylococcus aureus* [21]. It primarily functions by binding to bacterial cell

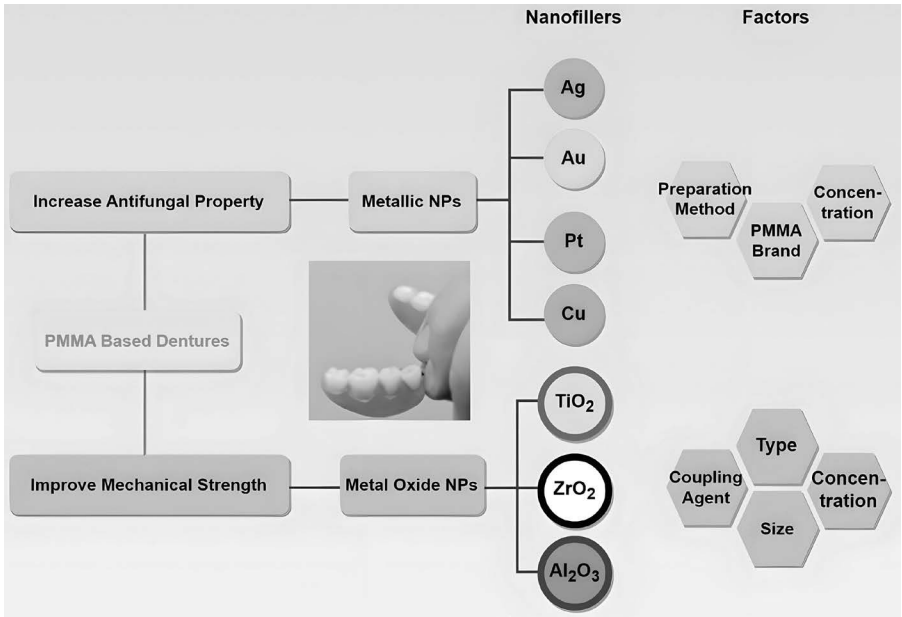

FIGURE 6.2 Different composition of PMMA nanocomposites with metallic nanoparticles or metal oxides.

membranes and cell walls, releasing Ag ions, inducing their disintegration, and effectively catalyzing the conversion of oxygen into reactive oxygen species (ROS), further exerting antibacterial effects. AgNPs also have antifungal properties, such as *C. albicans*, and kill fungus by disrupting cell membrane integrity. Other metal particles applied in PMMA modification include PtNPs, AuNPs, and CuNPs. Unlike AgNPs and PtNPs, AuNPs cause damage to fungal cells through "non-contact" interactions with microorganisms [22]. The antibacterial mechanism of CuNPs is largely attributed to the generation of ROS, which cause oxidative damage to cell structures, disrupt DNA replication, and deplete ATP within cells [23].

Metal nanoparticles can be directly added into PMMA powder or added to acrylic resin in the form of colloidal solution by volume/weight proportion to form composite materials. Metal nanoparticle-PMMA composites at appropriate concentrations can significantly reduce *C. albicans* adhesion and biofilm formation, showing promising efficacy in reducing the incidence of DS in limited clinical trials. At the same time, metal nanoparticles as impurities may pose risks of hindering PMMA polymerization and affecting its strength. Numerous studies are being conducted, aiming to find a balance between antimicrobial properties and mechanical performance to promote the clinical application of metal nanoparticle-PMMA composites. Additionally, some scholars express concerns about the toxicity reactions caused by metal nanoparticles released during use and ingested by the human body, suggesting further evaluation on the biocompatibility of metal nanoparticle-PMMA composites.

6.2.1.1 Antifungal Activity

In various studies, significant variations in the concentration of AgNPs have been used, ranging from 0.5% to 30%, all showing notable antibacterial effects. In the study by Takamiya et al., the addition of AgNPs (5 and 10 nm) at concentrations of 0.05% and 0.5% significantly reduced the number of *C. albicans* on the surface of acrylic acid compared to the control group [24]. Nam et al. demonstrated a significant reduction in *C. albicans* biofilm formation on surfaces with 20% and 30% AgNPs doped PMMA [25]. Torres et al. reported a significant reduction in both *C. albicans* adhesion and biofilm formation with the addition of 1% AgNP to PMMA [26]. These concentration differences may stem from variations in the chemical synthesis methods and stabilizers of AgNPs. Some experimental results indicate that under constant conditions, increasing AgNPs concentration enhances their antibacterial effectiveness. In Nam's study, AgNPs-PMMA samples showed bacteriostatic activity when the dosage exceeded 0.5%, with no colonies detected at concentrations of 2.0% and above, and no statistical difference in antibacterial efficacy observed between 24 hours and extended 72 hours incubation times. Chladek et al. found that the in vitro antifungal effectiveness (AFE) of samples ranged from 16.3% to 52.5%, and an increase in AgNPs content leading to an increase in AFE [27]. Nam noted that AgNPs-PMMA samples at 200–400 ppm exhibited significant anti-adhesive effects rather than strong bactericidal effects. Loading of AgNPs, PtNPs, and AuNPs reduced fungal adhesion rates by 61.6%, 58.6%, and 56.6%, respectively, compared to pure PMMA material, showing significant differences. Correa et al. found that the addition of 0.045 wt% CuNPs to PMMA exhibited high antibacterial activity against *C. albicans*, inhibited the transition from yeast to more virulent filamentous phenotypes, and conducted preliminary clinical trials confirming lower incidence and severity of DS in patients using CuNPs/PMMA dentures compared to those using traditional PMMA dentures.

Existing antibacterial studies mainly involve in vitro experiments, which have shown promising results but require further validation through clinical trials.

6.2.1.2 Flexural Strength

Dentures may fracture due to accidental impacts outside the oral cavity or experience fatigue fracture from repetitive chewing loads while working inside the mouth; thus, flexural strength is an important indicator of denture base materials. The addition of metal nanoparticles may affect the mechanical properties of PMMA materials. Takamiya conducted three-point bending tests on PMMA with the addition of 0.05% and 0.5% AgNPs, finding that the addition of nanoparticles had no significant effect on flexural strength, while 5% AgNP addition caused a significant decrease [24]. This was interpreted as the high concentration of nanoparticles diluting the concentration of cross-linking agents and interfering resin polymerization. Ashita's study also confirmed that 0.5% AgNPs did not have a significant impact on flexural strength [28]. Sodagar et al. systematically studied the effects of AgNPs incorporation on the mechanical properties of PMMA and found that the addition of AgNPs altered the bending strength of PMMA, which depended on the brand of PMMA and the amount of AgNPs [29]. In Selecta Plus samples, the presence of 0.05% and

0.2% AgNPs did not affect flexural strength, whereas in Rapid Repair samples, the unexpected addition of 0.05% AgNPs decreased the performance of the composite material. It was believed that at a concentration of 0.05%, the interaction between AgNPs and PMMA was minimal, and the nanoparticles could be considered impurities, reducing the mechanical strength of the composite material. With an increase in nanoparticle concentration (0.2%), chemical interactions between carboxyl groups formed within the polymer and silver overcame the aforementioned negative effects, resulting in increased flexural strength. Adamović tested the mechanical properties of AuNPs-PMMA composites with concentrations ranging from 0.12 to 0.74 wt%, where all groups showed slight decreases in flexural strength and elastic modulus values, but with no significant significance, while microhardness values increased proportionally with the concentration of AuNPs in PMMA [30]. Correa et al.'s study on CuNPs showed that the flexural strength and flexural modulus of 0.045 wt% nCu/PMMA did not differ significantly from pure PMMA.

In general, existing research suggests that the mechanical properties of metal nanoparticle-PMMA composites are influenced by various factors, including nanoparticle preparation methods, the way and the concentrations of acrylic resin incorporation, and differences in brands. Excessive filler concentrations can affect resin concentration and normal polymerization, leading to reduced mechanical strength, which is positively correlated with filler concentration. However, at appropriate concentrations, maintaining of original mechanical strength may be achieved through the formation of chemical interactions between carboxyl groups and metal ions. Therefore, the selection of appropriate formula to achieve a balance between antibacterial efficiency and mechanical performance still needs further exploration.

6.2.1.3 Biocompatibility

The unique physical and chemical properties of metal nanoparticles also bring limitations: they may cause toxic reactions in organisms. Studies have confirmed that AgNPs can be absorbed into the bloodstream through various pathways, such as nasal/oral mucosa, lungs, gastrointestinal tract, and skin, and distributed to organs and tissues including the lungs, kidneys, liver, spleen, testes, and others, ultimately causing toxic damage to these organs and tissues [31]. Some studies have even found that AgNPs can penetrate the blood-brain barrier and enter brain tissue, releasing Ag ions that are difficult to eliminate. This kind of continuous ions accumulation would ultimately induce neurotoxicity, which is more likely to occur in the elderly and infants.

Therefore, the application of metal nanoparticles in PMMA modification should be approached with greater caution. The dissolution of denture materials during decades of use causes releasee of metal nanoparticles into the oral cavity. These nanoparticles can penetrate oral mucosa or be swallowed and absorbed into the bloodstream, potentially affecting human health, especially in elderly patients. Currently, some scholars have implanted AgNPs-PMMA composites at the same concentration subcutaneously in rats and observed short-term (7 days) inflammatory responses, with normal tissue repair observed by 60 days [9]. Chen et al. reported severe inflammatory reactions in rat back muscles after AgNPs-PMMA composites implantation, with granulomas and abundant macrophages observed in tissues after

180 days [32]. Currently, there is still limited research in this area, mostly limited to in vitro experiments or animal models, making it difficult to accurately assess their biocompatibility. Future research is needed to establish scientific testing systems to evaluate the organ and neurotoxicity of PMMA modified with metal nanoparticles and their specific mechanisms, providing a theoretical basis for the safety of clinical application.

6.2.2 Metal Oxide Nanoparticles

The mechanical performance of PMMA dentures remains insufficient for clinical use, as fractures and breakages are common complications. These may occur inside the patient's oral cavity, typically at the midline of the denture base when under high chewing forces, or they may occur outside the oral cavity when removable dentures suddenly dislodge. It has been reported that removable dentures have an average fracture rate of 26.3% within three years [33]. After fracture occurs, repairs of old dentures may lead to decreased repair effectiveness or repeated fracture occurrences. In many cases, new dentures need to be made, which is costly and time-consuming for both patients and dentists. Therefore, researchers are attempting to incorporate high-strength metal oxide nanoparticles into PMMA to improve their mechanical properties and reduce the occurrence of denture fractures.

Commonly used metal oxides include TiO_2, ZrO_2, Al_2O_3, and other nanoparticles. TiO_2 has received much attention in recent years due to its high stability, white color, great corrosion resistance, high microhardness, and low cost. Even at low concentrations, TiO_2 nanoparticles can induce new physical, chemical, optical, and electrical properties, forming positively reinforced new nanocomposite materials. Additionally, TiO_2 is non-toxic and exhibits antibacterial activity against *C. albicans*, *S. aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Lactobacillus acidophilus*. ZrO_2 possesses excellent toughness, high mechanical strength, high hardness, high fracture strength, wear resistance, corrosion resistance, and good biocompatibility, making it a good choice for polymer reinforcement materials. Al_2O_3 is also being explored for PMMA modification due to its good biocompatibility, thermal conductivity, wear resistance, and corrosion resistance.

The characteristics of nanoparticles include small size and large specific surface area, leading to strong interactions with polymers at interface. Nanoscale metal oxide particles can bring new mechanical and physical properties to composite materials at extremely low concentrations, making polymer nanocomposites a promising new material. The performance of polymer-nanoparticle composite materials depends on the type, size, concentration of nanoparticles, the use of coupling agents (such as silanes), and the type of PMMA.

Previous research has reported that the addition of metal oxide nanoparticles can have either positive or negative effects on the flexural strength of acrylic resin, and it is mainly related to the concentration and dispersion degree of the nanoparticles. However, clinical practitioners have not yet reached a consensus on effective methods, and existing experimental results lack further validation through in vivo experiments. The main objectives of current research include selecting the best candidate materials and preparation methods to improve the mechanical properties of PMMA,

as well as conducting studies on hydrothermal aging, mechanical aging models, or clinical trials to confirm their clinical significance.

6.2.2.1 Mechanical Properties

The addition of metal oxide nanoparticles can improve various mechanical properties of PMMA materials. Research by Alrahlah et al. indicates that the inclusion of TiO_2 nanoparticles enhances the hardness and modulus of PMMA at the nanoscale [34]. Alamgir et al. prepared PMMA/TiO_2 nanocomposites with different percentages via melt blending, confirming improvements in hardness, modulus, creep recovery, and relaxation behavior [35]. Zidan et al. examined ZrO_2-PMMA composite materials with concentrations ranging from 0% to 10% (particle size 30–60 nm, surface treated with silanization) and found significant increases in flexural strength, flexural modulus, fracture, toughness, and surface hardness, with no significant decrease in impact strength [36]. The optimal concentration was found to be 3–5 wt% zirconium oxide. Similar results were obtained by Alhavaz et al. with unsilanized ZrO_2-PMMA composites (particle size 30 nm), observing significant improvements in flexural strength and surface hardness across all experimental groups, with 2.5% being the optimal concentration [37]. It has been repeatedly verified in some studies, with slight variations in the optimal concentration, generally ranging from 3% to 15%. Derazkola et al. prepared Al_2O_3-PMMA composites with up to 20 vol% Al_2O_3 nanoparticles with an average diameter of 50 nm, showing significant enhancements in flexural strength, hardness, and impact strength compared to pure PMMA [38].

There is currently limited comparative research on various additive particles, making it difficult to determine the differential effects of different particle types on the mechanical strength of composite materials. A comparative study of TiO_2 and Al_2O_3 nanoparticles showed that under the same conditions, TiO_2 added to PMMA exhibited more significant enhancements in impact strength and flexural strength compared to Al_2O_3. Therefore, TiO_2 seems to be a better choice than Al_2O_3 [39].

In contrast to the above positive results, some studies have shown that the addition of metal oxide nanoparticles may decrease the mechanical properties of PMMA, especially flexural strength. Sodagar observed a decrease in flexural strength when adding 1% and 0.5% TiO_2 to PMMA matrix, while Ergun found that the addition of 5%–20% nano-ZrO_2 to PMMA increased surface hardness but resulted in a gradual decrease in flexural strength with increasing nano-ZrO_2 content [40]. Akkus et al. observed a decrease in flexural strength when adding 1% and 3% 40–50 nm Al_2O_3 nanoparticles [41].

These negative results are believed to be resulted from the uneven distribution of nanoparticle fillers in the resin: agglomerated nanoparticles can be observed in the cross-sectional SEM images of many such materials. Because nanoparticles have a high specific surface area, surface energy, and chemical activity, they tend to aggregate, resulting in material defects and a decrease in the mechanical strength of PMMA composite materials. Increasing nanoparticle concentration exacerbates this phenomenon. Only well-distributed particles can form extensive contact areas and develop new properties in composite materials through stress transfer. Some existing studies suggest the use of coupling agents such as 3-methacryloxypropyltrimethoxysilane (MPTS) to prevent particle agglomeration. Silane coupling agents,

as surface treatments, can also promote adhesion between the inorganic surface and polymer molecules. Physical methods such as melt blending, high-energy ball milling, or ultrasonic vibration can also enhance the dispersion stability of nanoparticles in polymer matrices.

Exploration of material types, concentrations, and preparation methods is ongoing. For existing positive results, they are only preliminary results from in vitro studies that simulate the oral environment, unable to accurately reproduce all oral factors such as thermal fluctuations, chewing loads, chewing cycles, saliva pH, buffering capacity, and flow rate. Therefore, their clinical significance awaits further hydrothermal aging, mechanical aging model studies, or clinical trials.

6.2.2.2 Antifungal Activity

In addition to reinforcing PMMA materials, metal oxide nanoparticles also possess certain antibacterial properties. The incorporation of TiO_2 into PMMA polymer matrices has been shown to have antibacterial effects. PMMA samples containing 0.4%, 1%, and 2.5% TiO_2 nanoparticles significantly inhibited the growth of *C. albicans* [42]. Some studies have demonstrated that the antibacterial action of TiO_2 nanoparticles is due to the degradation of microbial cell components, particularly under ultraviolet irradiation, rather than the release of potential toxic compounds. Alrahlah et al. suggested that TiO_2 NPs also improve their antibacterial behavior by reducing bacterial adhesion to PMMA denture bases.

Research by Gad et al. showed that the addition of 7.5% nano-ZrO_2 significantly inhibited the growth of *C. albicans* on repaired denture bases and intact cold-cured resin surfaces, possibly due to the generation of ROS by nano-ZrO_2, leading to microbial cell membrane damage [43]. There is limited literature on the antibacterial effects of ZrO_2-PMMA, and a comprehensive assessment is still needed. Further antibacterial tests and clinical trials are required to validate these findings.

6.3 POLYMETHYLMETHACRYLATE/BARIUM TITANATE BIO-PIEZOELECTRIC COMPOSITES

Barium titanate ($BaTiO_3$, BT) is the first polycrystalline ceramic material with ferroelectricity ever discovered. Compared with other piezoelectric ceramics such as zirconate titanate that appeared earlier, BT has better biocompatibility, and particularly, this characteristic still exists even at concentrations greater than 100 μg/mL [44].

6.3.1 BT Nanoparticles

Piezoelectricity or piezoelectric effect (Figure 6.3) refers to the characteristic of certain dielectric materials that respond to mechanical stimulation by generating charges, and this process is reversible, which means that mechanical deformation (i.e. changes in physical size) can be induced by applying an electric field, or the corresponding amount of charge can be generated through mechanical changes [45]. As a bio-piezoelectric material, BT not only has the characteristics of antibacterial, anti-inflammatory, and promoting tissue regeneration but also has unique application advantages over other stimuli-responsive materials due to its inherent ability

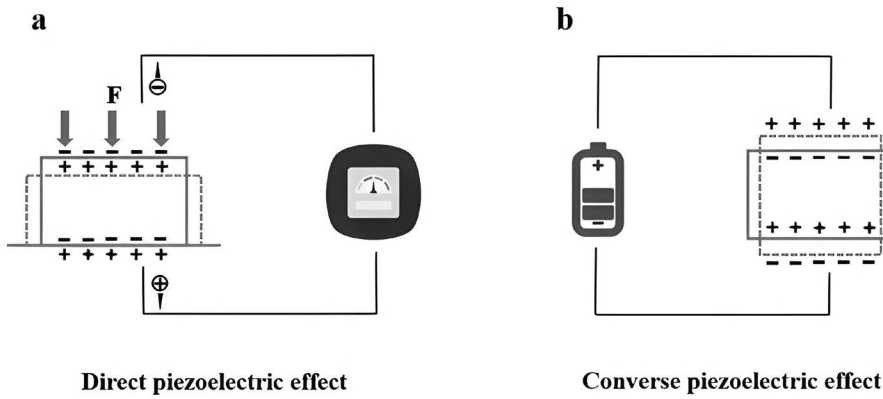

FIGURE 6.3(a, b) Schematic diagram of piezoelectric effect.

to generate charges [46]. Research has found that BT nanoparticles combined with hydroxyapatite can promote cell proliferation and differentiation, improve bone conduction and integration behavior of osteoblasts and bone cells, and can be used as implant materials in the field of bone tissue engineering [47]. In addition, incorporating BT nanoparticles as fillers into traditional dental resin composites also demonstrates antibacterial and remineralization effects [48].

6.3.2 Discovery and Development of PMMA/BT Biocomposites

PMMA, a biomaterial commonly used as a base for removable partial dentures and complete dentures, has shown an important problem in previous clinical applications due to its lack of antibacterial and antifungal effects. Due to the absence of ion charges, surface pores, and irregularity within the material structure, as well as a series of electrostatic and hydrophobic interactions, plaque biofilms exhibit a significantly easier colonization on the surface of PMMA [49]. The hydrophobic material surface of PMMA also facilitates the growth and proliferation of microorganisms on the hydrophobic cell surface, forming plaque biofilms, ultimately leading to inflammation and erythema on the oral mucosal area covered by dentures, known as Candida-associated denture stomatitis (CADS). CADS is a common recurrent disease, affecting up to 67% of the removable denture wearers, with a relatively high incidence rate among the elderly, women and immunosuppressed people [50]. Another common clinical situation is the fracture of PMMA denture base or artificial teeth [51], which can be attributed to the following factors, such as the base being too thin, the stress concentration area not being reinforced, the base and mucosa not tightly fitting due to various reasons, the artificial teeth not arranged on the top of the alveolar ridge, unbalanced occlusion, and insufficient mechanical properties.

In order to improve the biological activity and mechanical properties of PMMA materials and endow them with better antibacterial properties, PMMA/BT bio-piezoelectric composite materials have become an emerging direction in the field of material

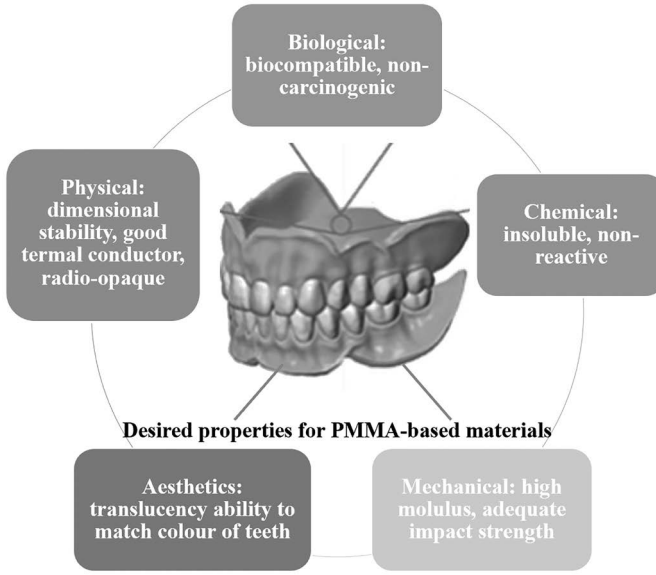
Biological: biocompatible, non-carcinogenic
Physical: dimensional stability, good termal conductor, radio-opaque
Chemical: insoluble, non-reactive
Desired properties for PMMA-based materials
Aesthetics: translucency ability to match colour of teeth
Mechanical: high molulus, adequate impact strength

FIGURE 6.4 Desired properties for PMMA-based materials.

research in recent years. According to the requirements of biological applications, PMMA-based composite biomaterials used as dental repair materials need to have the following properties (Figure 6.4): firstly, biocompatibility, that is, they should not cause any irritation, toxicity, or mutagenicity to oral tissues and will not have any adverse effects on surrounding tissues; secondly, certain chemical stability, which means that they should be highly insoluble in saliva and gingival crevicular fluid and firmly adhere to artificial teeth; thirdly, good mechanical properties (such as high elastic modulus, proportional limit, resilience, fatigue strength, and impact strength) to withstand chewing force without failure; in addition, other characteristics such as antibacterial properties, low specific gravity, thermal conductivity, and easy cleaning, as well as benefits for patient comfort. Therefore, the key points of research on PMMA/BT bio-piezoelectric composite materials lie in their mechanical properties, biocompatibility, antibacterial properties, and antifungal properties under chewing stress loading.

At present, a major challenge in the clinical transformation of PMMA/BT bio-piezoelectric composite materials is to verify whether the stress or mechanical load generated during physiological movements is sufficient to generate specific biological piezoelectric potentials. For example, studies have shown that higher potentials are beneficial for mammalian cell adhesion, proliferation, tissue regeneration, and mineralization, while lower potentials have a significant inhibitory effect on bacterial growth. Specifically, reinforced dental resin composites doped with 10% BT exhibit the best antibacterial effect at a potential of 1.2 pC/cm^2, which is in contrast to the maximum mineralization efficiency exhibited by composites doped with 60% BT at higher potentials (i.e. 3.2 pC/cm^2) [52]. In addition, an important research topic in this field is to characterize whether the same potential can kill Gram-positive bacteria,

Gram-negative bacteria, and yeast, as well as whether plaque biofilms can be eradicated or inhibited. The mechanisms and molecular signaling pathways by which these materials induce biological effects in microbial communities and human cells also need further clarification. At the same time, the long-term biocompatibility of most piezoelectric biomaterials still requires thorough research to evaluate. Moreover, in order to develop intelligent biocompatible piezoelectric composite materials, adjusting the piezoelectric properties of the original piezoelectric materials through chemical modification or biomolecular conjugation is an important approach for future research.

6.3.3 Synthesis Process of PMMA/BT Biocomposites

According to previous research, surface active initiators can be used to prepare polymer and BT particles with core-shell structure to improve the piezoelectric effect of BT particles. Chiozzi V et al. effectively confirmed that BT particles can adhere to gelatin cores and achieve significantly improved electrical response. Due to the lightweight and uneven particle size of BT shells, PMMA, a long and soft chain polymer compound, can theoretically serve as a core structure and become the preferred choice for preparing polymer and BT composite particles [53]. In a recent study, Liu et al. prepared PMMA/BT composites with core-shell structures of different relative molecular weights [54] and used the following four reagents: sodium dodecylbenzene sulfonate (SDBS), MMA monomer, ethanol, and potassium persulfate as surfactants, polymer monomers, solvents, and initiators respectively to prepare PMMA microspheres with a diameter of about 600 nm through lotion polymerization and use them as core materials for subsequent synthesis. The researchers used silane coupling agent KH570 to modify the surface of the monodisperse PMMA microspheres obtained from the above process and introduced reaction groups. Using titanium tetrachloride and barium hydroxide as raw materials, BT nanoparticles with a diameter of about 50 nm were prepared by solvothermal synthesis method. Finally, the required composite materials were prepared by self-assembly deposition method. Specifically, modified PMMA and BT nanoparticles were suspended in an ethanol aqueous solution, and the pH was adjusted to 2.8–3.0 with a 0.1 M HCl solution. Stir the obtained suspension at room temperature for another 3.5 hours and then dry it in a vacuum oven at 60°C for 10 hours. By controlling the relative amount of PMMA and BT, PMMA/BT composites with core-shell structures and different molecular weights were obtained in a mass ratio of 1:0.5–1:3.

6.3.4 Mechanical Properties of PMMA/BT Biocomposites

According to the guidelines of ISO 20795-1 [55], a three-point bending test is required to evaluate the flexural strength (also known as fracture toughness or transverse strength) of the materials. In an ideal situation, the denture base should have high bending strength to withstand the complex forces of chewing without permanent deformation or fracture. The research has shown that incorporating $BaTiO_3$ into PMMA improves the bending strength of composite materials and increases the tensile and bending modulus, exhibiting better bending resistance. Similarly, the microhardness value of composite materials is also higher than that of pure PMMA

samples, due to the high hardening value of dispersed phases and the limitation of uniform distribution of dispersed phases on matrix deformation. However, there are reports claiming that the enhancement effect of $BaTiO_3$ on the mechanical strength of composite materials is closely related to its doping concentration and proportion. High concentrations of $BaTiO_3$ nanoparticles can cause a decrease in the mechanical properties of PMMA composite materials, and this change may be influenced by factors such as filler distribution, particle size, and shape. In addition, denture bases made of pure PMMA do not have radiographic opacity, so they cannot be detected on radiographic images. What this means is that when dentures made of this material are accidentally inhaled or swallowed, it is not possible to perform internal localization and discrimination through radiographic methods. It is worth noting that the addition of $BaTiO_3$ particles endows the denture base polymer with radiation opacity, and the radiation opacity of PMMA composite materials is significantly improved. Therefore, PMMA/BT composite materials have high specific modulus and strength and have the advantage of enhancing X-ray opacity, making them a potential and reliable denture base material for application.

Besides, in the field of bone tissue engineering, the brittleness of $BaTiO_3$ limits its application as a bone substitute material for load-bearing areas, and the reduction of $BaTiO_3$ particles in composite materials reduces its piezoelectric effect on bone growth. For this purpose, a study has proposed a preparation method of directional freeze casting and self-solidification of bone cements to obtain 1–3 type PMMA/BT bio-piezoelectric composite materials with layered structure [56]. The $BaTiO_3$ particles are distributed in a layered manner and pass through the layers of the composite materials from bottom to top, significantly improving the piezoelectric performance of the composite materials. In addition, the dendritic ceramic bridge on the pore wall of $BaTiO_3$ can improve the compressive strength and elastic modulus of layered PMMA/BT bio-piezoelectric composite materials. More importantly, research has found that polarized-layered $BaTiO_3$ can induce osteoblast growth along the direction of the $BaTiO_3$ layer. When the width of the $BaTiO_3$ layer is within the range of 8–21 μm, osteoblasts grow well along the $BaTiO_3$ layer, which is of great value for the formation of biomimetic bone units [57].

6.3.5 Biocompatibility of PMMA/BT Biocomposites

In previous studies, $BaTiO_3$ has been proven to have excellent biocompatibility and can bind well with bone tissue, making it widely used as a material for bone repair and replacement. Ceramic materials doped with $BaTiO_3$ particles can also be used to make bone plates, artificial bones, artificial joints, and dental repair materials, etc. Zhou et al. described the formation of $BaTiO_3$ thin films and subsequently doped them with strontium (Sr) ions to improve the enhanced biological activity of bone integration [58]. Sr has been shown to activate various signaling pathways in osteoblasts and osteoclasts, such as calcium-sensitive receptors, inositol 1,4,5 triphosphate, MAPK-ERK1/2, and Wnt/NFATc, thereby promoting osteogenic differentiation of bone marrow cells and inhibiting osteoclast activity [59]. Due to the similar ionic radii (1.12 and 1.34 Å, respectively) and internal electronic structures of Sr and Ba, replacing Sr with $BaTiO_3$ structure is a reasonable choice. It can not only change the piezoelectric

properties of $BaTiO_3$ but also improve its biological activity. Since the substitution of Sr, the surface roughness of the composite material has further increased, with a microporous structure (approximately 30–300 μm), water contact angle (WCA) ($BaTiO_3$, 50°; Sr-$BaTiO_3$, 40°), reduced elastic modulus, and hardness ($BaTiO_3$, 1 GPa; Sr-$BaTiO_3$, 0.75 GPa). The film exhibits sustained release of Sr ions (3 ppm on day 1 and 4 ppm on day 14) and has been proven to be beneficial for cell adhesion in vitro, osteogenic differentiation, osteogenic response, and bone integration in vivo. It also has the advantages of lower mechanical properties (favorable for cell proliferation and osteogenesis) and WCA between 40 and 60°(enhanced cell adhesion) [60].

Likewise, PMMA has excellent biocompatibility, translucency, and inertness and has been widely used in the medical field for over 60 years. It is widely used in ophthalmic implants, bone cement, dental implants, hip joint implants, antibiotic carriers, and other fields. However, despite the excellent biological properties of both materials, there has been no in-depth investigation into the biological characteristics of PMMA/BT piezoelectric composite materials so far, and the relationship between biological activity and piezoelectric material properties is complex, as bone growth depends on a multifactorial process. Some researchers believe that bone cells can detect local stress, thereby enhancing bone remodeling in areas with higher stress levels. In addition, polarization may induce specific cellular pathways, thereby promoting bone growth. Further research on $BaTiO_3$ ceramics indicates that the ability to form hydroxyapatite depends on the polarity or partial charge of the surface. Positively charged surfaces do not exhibit biological activity, while negatively charged surfaces can bind cations, such as Ca^{2+}, followed by a typical process of chemically derived titanate forming hydroxyapatite.

6.3.6 Antibacterial and Antifungal Properties of PMMA/BT Biocomposites

Piezoelectric material is a type of material that can generate electric charges when subjected to mechanical loads. Some piezoelectric materials can sustainably generate charges under cyclic conditions of mechanical loading or unloading exceeding 12 million times. Assuming an average of 500k chewing cycles per year, this is equivalent to a shelf life of 24 years. Among them, $BaTiO_3$ is the earliest piezoelectric ceramic material discovered and introduced into the medical field. Previous studies have reported that $BaTiO_3$ has excellent osteogenic and antibacterial properties. Montoya et al. proposed for the first time the use of $BaTiO_3$ nanoparticles in dental composite resins [61]. Through a series of experiments, it was found that compared with the control group, a thick and dense layer of calcium phosphate mineral was formed on the surface of the experimental group resin, and the biofilm was significantly reduced (up to 90%). This is attributed to the piezoelectric charge generated on the surface of the composite resin when subjected to mechanical stimulation. On the one hand, it can attract mineralization ions with opposite charges through electrostatic interactions and promote mineralization, and on the other hand, it can repel bacteria through electrostatic interactions, prevent further adhesion, and ultimately inhibit biofilm growth. In addition, it can also promote the production of ROS by bacteria attached to the material.

In order to synthesize denture base materials with antifungal properties to reduce the incidence of CADS and overcome the limitations of traditional antifungal therapies, some studies have attempted to incorporate $BaTiO_3$ fillers into PMMA to prepare dental biocomposites. The experimental results show that cyclic mechanical loading (i.e. mechanobiological signals) is an environmental factor that affects the growth and morphology of *C. albicans* biofilms, manifested by corresponding changes in virulence, biomass, metabolic activity, and viable bacterial count, etc. The interaction between microorganisms and material surfaces is influenced by different biological material properties, including chemistry, roughness, morphology, surface energy, and charge. Specifically, for *C. albicans*, high hydrophobicity and surface roughness can enhance yeast adhesion and proliferation. It can be demonstrated through biofilm formation, phenotype transformation, and secretion of hydrolytic enzymes that this morphological transformation between single-cell yeast and multicellular filamentous hyphal growth plays an important role in the virulence of *C. albicans*. The cyclic loading (mechanical biological signals) on the surface of biomaterials causes this morphological transformation, leading to an increase in mycelial production and biofilm formation.

To further investigate the antifungal effects mentioned above, some scholars have conducted relevant studies on specific gene regulation. The results showed that the upregulation of HWP1 gene is related to the cell wall proteins required for normal hyphal development, while the downregulation of GSC1 gene indicates a decrease in the content of β-glucan after the yeast-to-hyphae transition. The regular deformation of the PMMA surface leads to an increase in biofilm formation and mycelial yield. Therefore, surface cyclic deformation is considered a new mechanical transduction signal that may trigger the transformation of yeast from a normal bacterial population to pathogenic and opportunistic infections, thereby making *C. albicans* pathogenic and virulent. As mentioned earlier, the upregulation of ALS1 gene is related to the formation of biofilms, and the upregulation of ALS1 gene in piezoelectric composite materials indicates that there is no correlation between antifungal mechanisms and reduced cell adhesion on the surface of biomaterials. The charge generated by $BaTiO_3$ piezoelectric fillers delays the formation of biofilm by inducing cell death, without affecting the adhesion of cells on the surface of biomaterials [62].

6.4 POLYMETHYLMETHACRYLATE/CARBON-BASED COMPOSITE MATERIAL

Diverse allotropes from carbon have been used as nanofillers in polymeric nanocomposites, including carbon nanotubes (CNTs), graphene (G), and its derivatives, graphene oxide (GO) and reduced GO (rGO) [63].

6.4.1 Graphene (G) and Its Derivatives

Graphene, composed of sp2 carbon atoms, is a new type of two-dimensional nanoscale material with excellent electrical, optical, and mechanical properties (Figure 6.5). It has a Young's modulus of approximately 1 TPa and a tensile strength of about 120 GPa [63]. Adding graphene to polymers can improve the mechanical properties

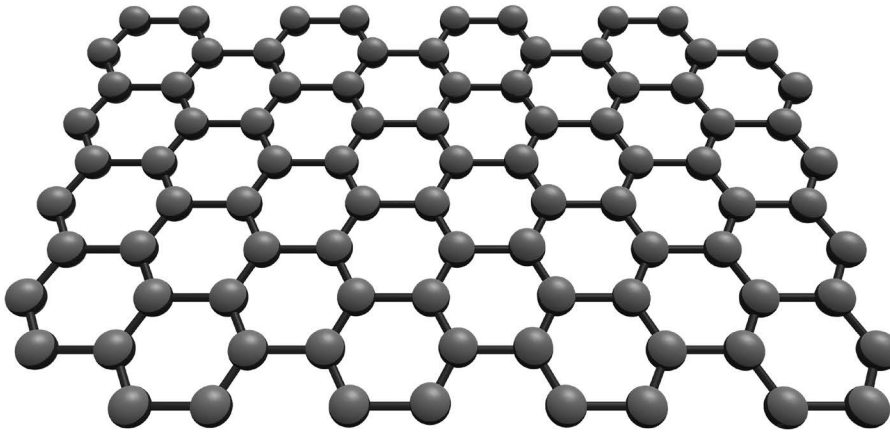

FIGURE 6.5 The structures of graphene.

of the material. However, graphene's strong van der Waals force makes it hydrophobic and prone to aggregation. GO, a derivative of functionalized graphene, is typically synthesized using strong oxidizing agents such as sulfuric acid or nitric acid through the Hummers method [64, 65]. GO is hydrophilic due to the abundance of oxygen-containing active groups such as hydroxyl (C–OH), carbonyl (C=O), and carboxyl (–COOH) on its surface and edges [66], enabling better dispersion and stability in polar solvents like water and easier preparation of composite materials with polymers. GO, as an enhanced filler, exhibits excellent mechanical properties, low friction characteristics, and relatively good biocompatibility in various composite materials, making its applications more extensive than graphene. Another derivative is rGO, which is synthesized by reducing GO. The reduction of oxygen results in the emergence of radicals, making rGO more stable. However, the reduction of oxidized functional groups can lead to a decrease in the surface area potential and solubility of the compound [67]. Graphene nanoplatelets (GNP), obtained through the exfoliation of graphite, possess high electrical conductivity and are composed of one to two layers of exfoliated compounds containing only carbon bonds. Their thickness ranges from 0.34 to 100 nm, and the lateral diameter ranges from 5 to 500 nm. GNP is insoluble in water but has a large surface area due to the dispersion of nanoparticles [68].

Graphene, known as the strongest material, is approximately 200 times harder than steel of the same thickness while being as light as carbon fiber and even more flexible. Since its discovery in 2004, graphene has been used in a wide range of research fields, from electronics and optoelectronics to biomedicine in 2008. The incorporation of graphene as an enhancer in oral applications of PMMA-based materials has attracted increasing attention.

6.4.1.1 Friction and Mechanical Properties

Graphene is often used as a reinforcement agent to improve the mechanical properties of materials. The addition of 0.1–0.75 wt% GO enhances the compressive strength of PMMA, while 0.5 wt% GO improves its hardness and flexural strength [68].

Alamgir et al. observed that the elastic modulus values of PMMA-G composites were higher than those of traditional PMMA. The improvement in the mechanical properties of PMMA after the incorporation of GO is attributed to the favorable formation of chemical bonds between graphene and the polymer matrix due to the functional groups [69]. Miquel Punset et al. added 0.027 wt% of 100–200 nm rGO to PMMA, and this composite material can be used to make prostheses. The elastic modulus increased from 2.01 to 2.89 GPa, the mechanical compressive strength increased from 129.43 to 140.23 MPa, and the friction coefficient decreased from 0.4032 to 0.4001. These enhanced mechanical properties improve the wear resistance of the composite material. However, when the concentration of graphene in PMMA exceeds 0.35 wt%, the color of the composite material becomes darker, making it difficult to achieve good aesthetic restoration [70]. The percentage of 0.027 wt% of graphene ensures low material costs and satisfactory aesthetic performance for oral restoration. Therefore, the application of graphene-reinforced PMMA-based composites in the oral field requires achieving the right balance between the desired increase in mechanical properties and compliance with aesthetic standards.

Low concentrations of graphene derivatives promote the improvement of mechanical properties. However, at high concentrations, the dispersibility of GO worsens, leading to agglomeration in the polymer matrix. The high viscosity of the mixture reduces the flexural strength and hardness of PMMA, negatively affecting its mechanical properties. Paz et al. added GO to PMMA and found that the mechanical properties of 0.25 wt% GO-PMMA were the strongest, while those of 1.0 wt% GO-PMMA were weakened. When rGO is incorporated into PMMA at concentrations greater than 1 wt%, the polymer tension decreases, leading to increased brittleness and compromising its clinical durability [68]. Graphene synthesized in the form of nanosheets has fewer layers, allowing the compound to disperse and insert better between polymer chains, increasing the stiffness of the material [68]. Methods such as ultrasonic treatment, silanization, and carboxyl association can enhance the dispersibility of these particles, thereby improving the properties of the polymer [71]. Therefore, further research is needed to determine the optimal form of graphene addition and the range of optimal enhancement percentages.

Graphene-reinforced PMMA-based composites for oral restoration are being commercialized. Different proportions of fibers provide a wide range of colors, offering good aesthetic effects for restorations. G-CAM, produced by Graphenano Dental, is a PMMA doped with graphene. It has a flexural strength of 140±7% MPa, an elastic modulus of 3200±7% MPa, a compressive strength of 155±5 MPa, and a Shore hardness of 88 HD. Luca Ortensi et al. evaluated the fracture strength of fixed bridges prepared from traditional PMMA and G-CAM before and after aging [72]. Before aging, PMMA exhibited higher fracture strength, possibly due to the fact that although graphene fillers improve the toughness, flexural strength, wear resistance, and elastic modulus of the composite material [8], they also reduce material deformation under compressive loads, increasing brittleness. The aging process has a significant impact on the mechanical properties of PMMA, while G-CAM seems to be unaffected by the aging process [72]. Another study evaluated the fracture strength of full crowns made from five different materials [73]. The results showed that the fracture strength of graphene-reinforced PMMA-based composites was superior to

that of traditional PMMA and comparable to cubic zirconia, especially after aging. Azevedo et al. completed a maxillary full arch restoration using a graphene-reinforced PMMA-based composite [74]. After a follow-up period of eight months, no mechanical, aesthetic, or other complications were observed. This suggests that graphene-reinforced PMMA-based composites are a good choice for the fabrication of permanent restorations. However, further assessments with a large number of aging cycles, different restoration designs, and longer follow-up periods are needed to evaluate the mechanical properties and color stability of these materials, obtain rigorous scientific support, and determine the benefits of these new techniques and materials.

6.4.1.2 Antibacterial Properties

Studies have shown that graphene-based nanomaterials can produce broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, and even fungal pathogens, through various mechanisms. GO is considered one of the most effective emerging nano-antibacterial materials due to its multiple antibacterial mechanisms, including edge cutting effect, cell embedding ability, and oxidative stress response. Lee et al. used GO nanosheets (nGO) to improve the plaque adhesion of PMMA. Their results showed that the incorporation of nGO reduced the adhesion of *C. albicans*, *E. coli*, *S. aureus*, and *Streptococcus mutans* [75]. Bacali et al. added graphene Ag nanoparticles (G-AgNp) to PMMA to evaluate the antibacterial properties, cytotoxicity, monomer release, and mechanical properties of the material [76]. The results indicated that the G-AgNp group exhibited good antibacterial effects against both Gram-positive and Gram-negative bacteria, with better antibacterial effects against *S. aureus* than traditional PMMA. *E. coli* was also sensitive to G-AgNp.

Most antibacterial agents, while exerting antibacterial effects, inevitably have toxic side effects on normal cells. Therefore, it is necessary to evaluate the biocompatibility and cytotoxicity of graphene-based substances. The biocompatibility and toxicity of graphene and its derivatives are dose-dependent. Studies have shown that when the concentration of GO is below 20 μg/mL, its toxicity to fibroblasts is minimal [77]. Some scholars believe that when GO is added to polymers and encapsulated within the matrix, making it less soluble, the direct contact between GO and cells is reduced, thereby reducing its cytotoxicity. Overall, graphene and its derivatives are promising antibacterial fillers for PMMA.

6.4.2 Carbon Nanotubes

CNTs were first discovered by Iijima in 1991. CNTs are seamless, hollow tubes with a nanoscale outer diameter formed by rolling up graphene sheets composed of carbon six-membered rings. The ends of CNTs are closed by "carbon caps" formed by half-fullerene spheres containing pentagons/heptagons. CNTs are classified as single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs) based on their wall thickness. MWCNTs are multi-layer rolled-up graphene sheets, while SWCNTs are nanocylinders constructed from a single graphene sheet (Figure 6.6) [63]. Manufacturing techniques for CNTs include arc discharge, laser ablation, and chemical vapor deposition (CVD). Among them, CVD is widely used due to its relatively simple and flexible process, low cost, and ease of operation [78]. Owing to their excellent mechanical

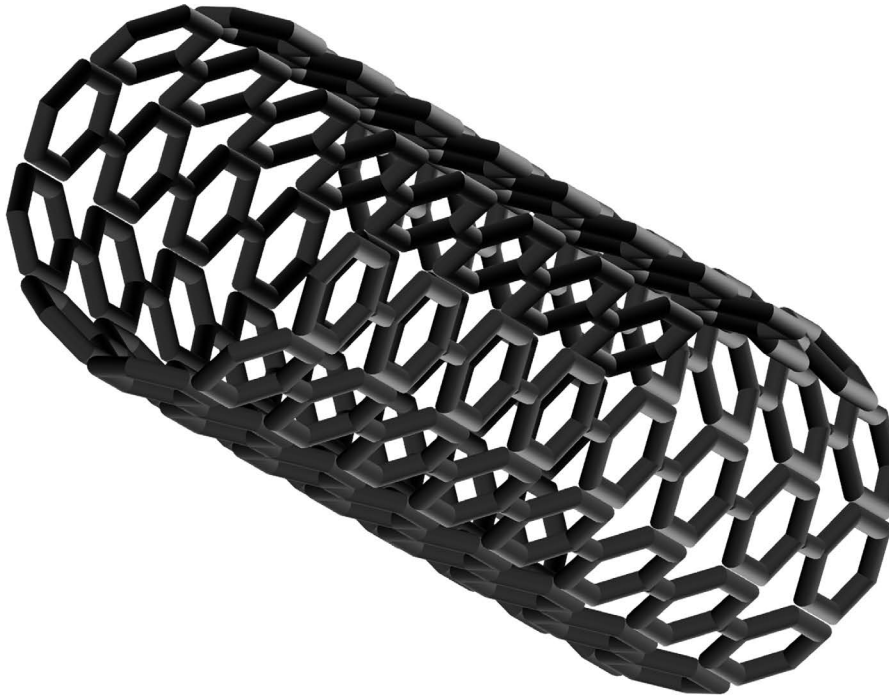

FIGURE 6.6 The structures of SWCNT.

and electrical properties, including high strength (tensile strength of approximately 100–300 GPa), high stiffness (elastic modulus up to 1 TPa), remarkable flexibility and elasticity, high conductivity, and high aspect ratio, CNTs have long been considered ideal fillers for polymer composites [63, 66, 78]. Incorporating CNTs into polymer matrices can produce composites with excellent material properties, increasing the modulus, strength, and conductivity of the material [78].

Currently, the limitations of CNTs in enhancing polymer performance mainly stem from two issues: (1) the difficulty in dispersing CNTs in polymers. CNTs are hydrophobic and conductive. When preparing composites with high nanotube loading levels, the large surface area of CNTs leads to high viscosity of the nanotube/resin combination, making it difficult to disperse the nanotubes [78]. (2) Insufficient bonding at the interface between CNTs and polymers. When there is no chemical bonding at the CNT-polymer interface, adding carboxyl or amide functional groups to CNTs is a reasonable method to promote CNT-polymer interface reactions. Chemical, electrochemical, or plasma treatments can be used to place different functional groups on MWCNTs [79]. Another method is to modify the surface of CNTs using oxidation or silanization processes with low-pressure oxygen plasma treatment. Controlling particle size distribution and dispersion is an important factor in the production of composite materials. Therefore, future research directions lie in the uniform dispersion of CNTs in polymer matrices and the interaction between CNTs and polymer matrices.

6.4.2.1 Mechanical Properties

CNTs possess excellent mechanical and electrical properties. When comparing equal weights, CNTs are 10–100 times stronger than steel. CNTs are sturdy, elastic, and lightweight. Adding CNTs to a resin matrix can enhance the material's strength and elasticity, while only causing minimal losses in toughness [80]. Currently, the preparation of polymer composites primarily involves liquid-phase blending, melt blending, and in-situ polymerization [81]. Russell Wang et al. prepared MWCNTs-PMMA nanocomposite resins by mixing PMMA liquid-phase monomers with MWCNTs through high-power ultrasonic vibration and characterized their mechanical properties [82]. The addition of 0.5 and 1.0 wt% MWCNTs significantly improved the bending strength and elasticity of PMMA. Compared with the control group, the bending strength of the 0.5% MWCNTs group increased by an average of 9.3%, while the 1% MWCNTs group increased by an average of 3.9%. The elasticity of the 0.5 wt% MWCNTs group increased by an average of 15.9%, and the 1 wt% group increased by an average of 29%. Kim et al. studied the mechanical properties of PMMA doped with 0.25–2.0 wt% carboxylated multi-walled CNTs and found that the fracture strength of 1 and 2 wt% MWCNTs PMMA increased, indicating an increase in resistance to external deformation energy before PMMA fractures. However, the impact strength of all types of specimens failed to meet the minimum requirement [83].

The superior mechanical properties of CNT composites compared to traditional polymer composites are attributed to CNTs' extremely high inherent strength and modulus. CNTs are hollow cages with a closed topological configuration, able to demonstrate elasticity through volumetric changes, thus tolerating greater tensile strain without brittle behavior, plastic deformation, or bond breakage. The stress transfer efficiency is approximately 10 times higher than traditional additives. Additionally, the addition of CNTs often alters the deformation mode of PMMA fibers. Pure PMMA fibers undergo polymer necking under increasing tension, leading to fractures at relatively small strains. Incorporating CNTs into polymers can significantly enhance their resistance to strain. This is not only due to MWCNTs reinforcing fibrils but also their ability to bridge cracks. When cracks form in polymers under stress, CNTs effectively bridge them, strengthening the fracture line, thereby enhancing the fatigue properties of polymers and reducing the degree of plastic deformation in the PMMA matrix [84, 85].

The dispersion state of MWCNTs is a crucial factor determining the extent of mechanical property enhancement. MWCNTs often agglomerate during their addition to polymers such as CNT-polymer composite resins. Methods using ultrasonic vibration or chemical modification have been proposed to uniformly disperse CNTs into the polymer matrix. Russell Wang et al. found that the 2 wt% MWCNTs group exhibited relatively poor mechanical properties due to MWCNT agglomeration. Future research could explore adding surfactants to PMMA during the mixing process to provide a better solution for the uniform dispersion of MWCNTs into polymer materials [82]. According to Raman spectroscopy and dynamic load experiments, although there is an improvement in mechanical properties, the binding between MWCNTs and the PMMA matrix is not sufficiently strong. Therefore, future research directions involve surface modification of MWCNTs to promote better interactions with polymers [82].

6.4.2.2 Antibacterial Properties

Silver (Ag) nanoparticles are effective antibacterial fillers, and Ag nanoparticle CNTs can produce unique fillers with antibacterial activity. Compared to traditional PMMA, Ag nanoparticle CNT-PMMA exhibits higher impact strength, hardness, and antifungal activity against *C. albicans* [86]. Kim et al. added carboxylated CNTs to PMMA, increasing their dispersion in the solution. The results showed that CNT-PMMA exhibited anti-adhesion effects against all studied microorganisms, and these effects increased with increasing CNT content. The adhesion forces of 1wt% MWCNTs-PMMA composites for *C. albicans*, *S. aureus*, and *S mutans* were reduced by 35–95%, and they were non-toxic to keratinocytes [83]. This study reveals the anti-adhesion effects of CNT-PMMA composites without adding any antibacterial drugs, biomolecules, or ions (such as Ag, Cu, Gd) against microorganisms. CNT-PMMA composites have potential practical applications as future antibacterial materials for preventing complications caused by microorganisms (i.e. Candida infections) in the oral environment.

6.5 POLYMETHYLMETHACRYLATE/CALCIUM PHOSPHATE BIOLOGICAL COMPOSITE BONE CEMENTS

Calcium phosphate cements (CPC) refer to some specific bioactive materials with biocompatibility, bone conductivity, and biodegradability, including calcium phosphate compounds such as hydroxyapatite (HA), calcium phosphate (CaP), tricalcium phosphate (TCP), and tricalcium phosphate.

6.5.1 Calcium Phosphate Cements

The chemical composition of CPC materials is similar to that of natural bones, which means that the Ca^{2+} and PO_4^{3-} ions released after degradation of the materials can promote bone conduction and osteogenic reactions. As a substitute for bone transplantation in periodontal and cartilage regeneration, and as a potential carrier in controlled release systems, calcium phosphate material has always been of great concern [87]. CPC materials are generally composed of one or more powder phases comprising calcium phosphate combined with a liquid phase, which is usually water or aqueous solution. Although CPC materials have been proven to have excellent biocompatibility and bone conductivity, there are also some limitations in their clinical applications that limit the expansion of their indications [88]. For example, the curing time is long, and the heat release during the curing process is relatively low (equivalent to room temperature), resulting in relatively poor adhesion and strength, and easy disintegration from the bone. In addition, the inability of solid-liquid mixtures to form also makes clinical applications difficult.

6.5.2 PMMA Bone Cements

PMMA, as another type of bone cement biomaterials, is widely used in the fields of ophthalmology, dentistry, and orthopedics (Figure 6.7). In orthopedics, PMMA is used for total hip replacement, spinal fracture fixation, internal fixation plates (i.e.

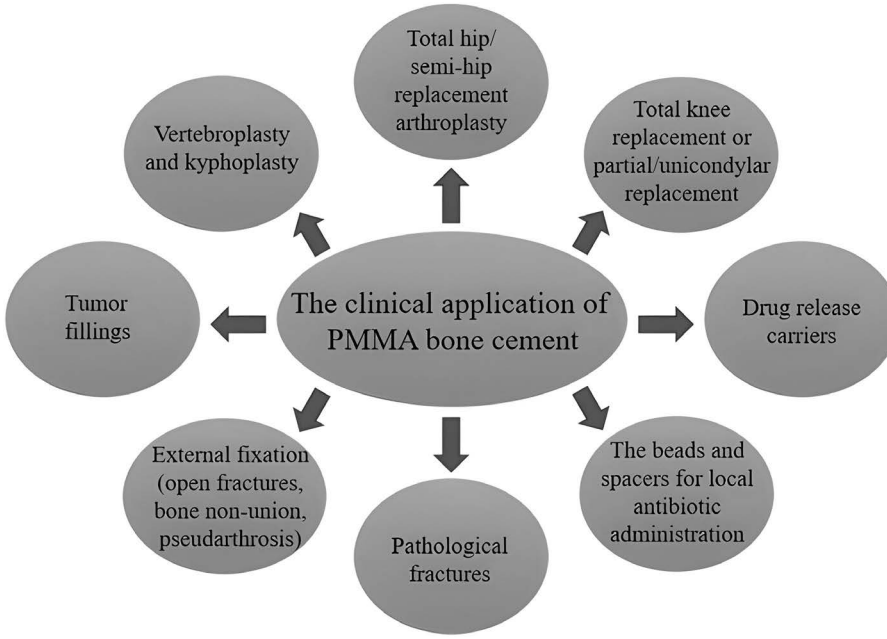

FIGURE 6.7 Clinical application of PMMA bone cements.

adhesive plates), and as a permanent bone substitute in the treatment of pathological fractures. PMMA is also composed of a powder phase and a liquid phase, with the powder phase containing 10–15 wt% barium sulfate/zirconia, 82–89 wt% PMMA, and 0.5–2.6 wt% methylbenzoyl peroxide as catalysts for polymerization reactions. The liquid phase consists of 98 wt% MMA monomer and 2 wt% N,N-dimethylpara toluidine to accelerate polymerization. PMMA has good compressive strength (about 80 MPa), a solidification temperature of about 80°C, and a solidification time of about 2 minutes. It is easy and fast to form during solidification and can also be made into specific shapes according to the requirements of the implant or polymerized in situ during surgery [89]. However, PMMA is neither biodegradable nor can it induce bone regeneration or bone conduction, and its clinical applications are limited to joint replacement, local bone defect filling, and supporting effects, such as vertebroplasty.

6.5.3 Discovery and Synthesis of PMMA/CPC Biocomposite Bone Cements

Therefore, based on the advantages and disadvantages of the two materials mentioned above, many studies have gradually attempted to incorporate CPC into PMMA materials to overcome their limitations when applied alone and combine the strengths of both to obtain PMMA/CPC biocomposites with optimized mechanical properties, biological activity, and tissue regeneration performance.

So far, most of the researches on modified PMMA/CPC biocomposites both domestically and internationally are still in the laboratory stage and have not been widely applied in clinical work. There are several reasons worth considering:

1. Whether organic materials, inorganic materials, or bioactive materials are introduced into PMMA, the number of experimental samples is small, and there is a lack of sufficient clinical trial data to ensure the quality of the materials.
2. Although some composite materials have significant effects, due to their complex and rigorous preparation processes and high requirements, it is difficult for most medical device consumables production enterprises to carry out mass production.
3. The introduction of bioactive materials (such as hydroxymethyl chitosan) can help improve the porosity of traditional PMMA bone cements. To some extent, the bioactivity of new materials can induce bone tissue growth. However, on the other hand, if the newly introduced components degrade prematurely in PMMA, it may lead to incomplete growth and development of the new bone, without forming a reliable connection interface between the implant and autologous bone, resulting in recurrent fractures or loosening or fracture of implanted materials.

To meet the clinical needs of surgical use such as filling bone defects and preventing infections, the development direction of the researches on PMMA/CPC biocomposites requires that they have appropriate mechanical properties, no biological toxicity to the human body, and good biological activity, which can tightly bond bone cements with human bone tissue and promote the growth of new bone tissue in the human body. For the clinical transformation of this type of biocomposite materials, more preclinical trial data and long-term follow-up observations will be a research focus worth paying attention to in the future.

Among all CPC materials, HA is an effective bone tissue regeneration material due to its biocompatibility, bone conductivity, biodegradability, low cost, and easier formation of apatite. It is also considered the most widely studied and promising bone-like material. Research has shown that the addition of polymer often enhances the mechanical stability of HA in scaffold formation. Therefore, this section takes HA as an example to briefly discuss the synthesis process of PMMA and HA biocomposite materials in the latest research. In the review by Szulc M et al. [90], a synthetic pathway was mentioned, with the aim of preparing a composite scaffold composed of chitosan grafted PMMA and HA through hydrothermal treatment using a blending method. Experimental results showed that this composite material can be used as a scaffold for inward growth of bone cells and for drug delivery in bone repair processes. To further simulate the layered structure of natural bones, Tabrizian P et al. investigated the effective processing parameters for obtaining the optimal mechanical properties of PMMA/HA composite materials through bidirectional freeze-casting method [91]. The technical details of bidirectional freeze casting are as follows. After the sample is frozen, the ice formed in the frozen sample is sublimated at −60°C for at least 48 hours under

a vacuum pressure of 0.03 mbar. In order to control the ceramic part in the final composite material, the highly arranged layered ceramic support is densified by hydraulic press and finally sintered using a calcination furnace with an oxidizing atmosphere. Wijesinghe WPSL et al. [92] also proposed a synthetic pathway that can be used for industrial production, using readily available and widely distributed dolomite as a calcium source to synthesize HA-PMMA composite materials. Firstly, calcined dolomite (CaO·MgO) was mixed with 0.5 M sucrose solution for 6 hours, and the mixture was filtered under suction and the solution was collected. Then, potassium persulfate was dissolved in a 0.5 M calcium mustard solution and heated to 80°C while stirring. MMA monomers and 0.3 M ammonium dihydrogen orthophosphate were added to the reaction mixture using two drip hoppers, stirred for 12 hours, and filtered under suction to obtain precipitates. After washing and drying, PMMA/HA nanocomposites with an average particle size of about 30 nm were finally obtained.

6.5.4 Mechanical Property of PMMA/CPC Biocomposite Bone Cements

Due to the limited mechanical properties and poor compatibility with bones of PMMA materials, their clinical uses are accompanied by complications, including the brittleness and shrinkage, the generation of voids during processing, the lack of adhesion to bones, and possible damage to the exothermic polymerization reaction of bone tissue. To improve the above defects, some researchers have attempted to synthesize bioceramic-reinforced polymer composites, incorporating HA doped PMMA as potential bone cement materials. In fact, adding HA to bone cements can improve biocompatibility and enhance the mechanical properties of the cements. Depending on the amount of HA added, the mechanical and thermal properties of the composite materials may differ. According to reports, the size and surface characteristics of particles can increase or decrease the mechanical properties of bone cements. Previous studies have pointed out that adding up to 15 wt% HA to commercially available PMMA-based bone cements increased the flexural modulus, but the tensile and compressive strength of PMMA-based cements remained unchanged [93]. According to observations, adding 40 wt% HA can improve the fracture toughness of HA-reinforced PMMA. Fouly A et al. [94] investigated the mechanical and tribological properties of PMMA reinforced with HA nanoparticles with different low load fractions (i.e. 0.2–0.8 wt%). The results indicated that as the concentration of HA nanoparticles increased, the compressive strength, toughness, and ductility of PMMA/HA composite materials were improved to a certain extent. In addition, tribological tests showed that an increased weight fraction of nanoparticles leaded to a significant reduction in friction coefficient and wear loss. Tan QC et al. [95] synthesized a novel bioactive GO-functionalized composite material based on PMMA. The results showed that the cement exhibited excellent compressive strength (>70 MPa), longer processing time, lower set temperature, and better attachment of osteoblasts. Researchers have also proposed that, unlike the tensile strength of cement, adding HA can increase

compressive strength and fatigue life. Wang H et al. [96] and Shirdar MR et al. [97] studied the effects of particle size and shape and found that the smaller the particle size, the greater the aspect ratio, and the better the mechanical properties of the composite materials.

In the latest study by Lei Chen et al. [98], it was found that the transformation of CPC materials into rigid mechanical support networks and the chelation between organic and inorganic materials enhanced the mechanical properties of composite materials after immersion. The compressive strength after immersion reached 62.97 ± 0.97 MPa, which was 27.65% higher than before immersion. After soaking for nine days, the degradation rate of the composite material reached 13.76 ± 0.23%, which was 16.4% higher than CPC. Similarly, Elakkiya K et al. [99] found similar composite structures, where small CaP particles agglomerate within the pores of PMMA, while larger CaP particles are partially embedded in the PMMA matrix and partially exposed in the pores. The addition of CaP particles has no effect on the maximum polymerization temperature of porous PMMA but reduces the porosity and average pore size. Both types of CaP particles enhance the mineralization ability of PMMA cement without affecting its mechanical properties. Sa Y et al. also made similar findings [100], confirming that porous PMMA effectively loads CaP by evaluating the physicochemical and mechanical properties of porous PMMA cement loaded with different amounts of CaP, and that the percentage of CaP or soaking time does not significantly change the mechanical properties.

In addition, some researches attempted to incorporate α-TCP particles into PMMA bone cements as a dispersed phase. After observing the microstructure of the composite material, it was found that PMMA formed a matrix-like structure with a pore size of about 100 microns, containing TCP clusters. TCP molecules aggregated to form a porous network, with an average mesoporous diameter of about 0.1 microns. By further evaluating the dynamic elastic modulus, compression, and tensile strength of composite materials, this study confirms that the composite materials retain good mechanical properties. In recent studies, some scholars have used TCP and chitosan as additives in pure PMMA bone cements to prepare bioactive bone cements and simulated the composition of human bone using the ratio of TCP and chitosan content, namely 65 wt% inorganic component and 35 wt% organic component. A series of physicochemical and mechanical properties were evaluated through in vitro testing, including setting time, ultimate compressive strength, compressive modulus, degradation behavior, and shear stress. The results showed that adding TCP and chitosan powder as a dispersed phase reduced the compressive strength of acrylic bone cements in the early stage, consistent with the research findings of Korzh M et al. [101]. Some researchers have pointed out that this phenomenon is due to the structural problem of "stress shielding". The two materials with significant differences in mechanical properties will lead to significant stress discontinuity inside the composite materials. When pure acrylic bone cements are used in orthopedic surgery, it may lead to structural instability in the long run, while biological composite bone cements will experience less stress shielding, which is more conducive to long-term structural stability.

6.5.5 Biological Activity of PMMA/CPC Biocomposite Bone Cements

According to the application requirements of biomaterials, ideal composite bone cement materials should have the following characteristics:

1. Biocompatibility, the ability to perform intended function in the body without causing any adverse side effects;
2. Biological activity, additional ability to chemically bind with surrounding tissues and participate in specific biological phenomena (such as ion exchange);
3. Bio-absorbability, the ultimate sability of implanted materials to be reabsorbed over time by actively participating in physiological turnover reactions, which is beneficial for the formation of new tissues.

For pure PMMA materials, they only have good biocompatibility and do not possess biological activity. Therefore, the research focus of PMMA/CPC biocomposites is whether the addition of calcium phosphate materials endows the composite materials with long-term and stable biological activity. Kang IG et al. attempted to use HA microspheres as additional fillers to enhance the biological function of PMMA/HA composite bone cements without sacrificing the existing mechanical properties [102]. The results indicated that PMMA/HA composite materials were more conducive to cell adhesion and spreading, especially on the surface of HA microspheres, where cells exhibited filamentous extension and branching. In addition, the newly formed bone tissue around and inside the PMMA/HA composite materials was far more than that of the PMMA material. As the implantation period of the PMMA/HA composite materials increased, the bone volume also showed a significant increase.

As a bioinert material, PMMA bone cement cannot form a tight bond with human bone tissue, nor can it induce bone tissue growth. Therefore, endowing traditional PMMA bone cements with biological activity through modification is one of the goals that researchers are striving for. The combination of PMMA and β-TCP is the most commonly used bone transplant mixture in orthopedic applications. By adding β-TCP to PMMA, a porous structure of bone cement is formed, providing an opportunity for blood vessels and bone cells to colonize the remaining bone space surface after bone cement resorption. This also allows osteoblasts to uniformly regenerate bone tissue at the bone cement interface. Cheah C W et al. explored the synthesis and characteristics of PMMA/β-TCP composite bone cements [103], and the composite materials of different sizes were implanted into rabbit bone tissue, confirming that the growth of new bone tissue was significantly promoted. Through histological analysis, it was concluded that in the bone tissue area of rabbits implanted with PMMA/β-TCP composite cements in the experimental group, there was no inflammation or bone degradation at the implant boundary. More importantly, after long-term observation, it was found that newly formed bone tissue gradually covered the surface of the implant materials.

In addition, studies have explored the effect of PMMA/HA composite materials on the response of osteoblasts. Through immunohistochemical examination of extracellular matrix production, it was found that osteoblasts cultured on PMMA/HA composite materials exhibited more pronounced tissue fibronectin network patterns. The histological staining of mineralization was examined using confocal microscopy, and the

results showed that compared to PMMA, the mineralization degree of nodules formed on the surface of PMMA/HA biocomposites was much higher. In summary, these results indicated that adding HA to the PMMA matrix can improve osteoblast response compared to using PMMA alone. Therefore, incorporating HA into PMMA matrix may be an effective way to provide better biological activity for PMMA materials.

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7 Development of Biocomposites-Based Prosthesis Foot Using Additive Manufacturing Processes

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7.1 INTRODUCTION

The usage of natural fibres has been steadily replacing synthetic polymers, which are derived from non-renewable resources and petroleum-based products, due to their contribution to greenhouse gas emissions in the environment [1–3]. Due to their affordability, environmental sustainability, strong mechanical properties, lightweight nature, and ability to decompose naturally, natural fibres serve as a superior alternative to synthetic fibres. Natural fibres have several benefits, including their low density, renewable nature, easy disposability, high stiffness, improved mechanical qualities, and high specific energy. Biodegradable composites are produced by strengthening natural fibres, derived from plants and animals, with biodegradable polymers over the course of a few decades. It is used in many sectors such as the automotive and construction industries. These materials are used in automobiles to improve fuel economy by decreasing weight density. Brake shoes, trays, doors, and printed sheets are manufactured with bio-composite materials [4–6]. Plant-derived organic fibres have been used in many sectors including textile manufacturing, automotive production, construction, sports equipment, and medicine. The biocomposites include natural fibres derived from agricultural goods and by-products, which are then blended with various polymer-based matrices. The production of bio-composites was achieved by several processing methods, such as compression moulding, injection moulding, resin transfer moulding, sheet moulding, hand lay-up, filament winding, extrusion, and pultrusion processes. These techniques enable the natural fibres to strengthen in many forms, such as loose fibres, nonwoven mats, aligned yarns, and/or woven textiles. This allows them to be positioned in the correct direction to get certain mechanical qualities in the end product [7–9]. During the creation of biocomposites, interfacial bonds will form between two or more materials, and their cohesive force will also be present. The physical and chemical processes

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strengthened the linkages at the interface between the surface of the fibres and the biopolymer matrix [10–12]. As per the findings of Guna et al. [5], the tensile and flexural characteristics of polypropylene-based composites showed an upward trend as the ratio of sabai grass rose. The fibre bundles derived from the sabai grass exhibited a tensile strength of 493 MPa and a tensile modulus of 21 GPa. The vacuum bagging method [13–15] has been used to create a below-knee prosthetic socket utilising flax fibres and cotton fibres. The augmentation of the fibreglass content in the polyester composite led to an enhancement in the mechanical characteristics, including ultimate tensile strength, Young's modulus of elasticity, and elastic strain, with the exception of impact strength. The ideal volume percentage of glass fibres for the composite is 0.25 [16]. Kumar et al. [9] constructed a customised ankle foot orthosis with a carbon fibre strut. They observed that the carbon fibre strut effectively stores and releases energy during different stages of the gait cycle, hence enhancing ankle power by 36.84% and 60.57%. The maximum range of motion during the push-off phase in individuals with drop feet during the walking cycle was also improved. Jweeg et al. [10] constructed transtibial prosthetic sockets by combining layers of perlon and carbon fibres with polyvinyl alcohol (PVA) bags, resulting in hybrid laminates consisting of six perlon layers and four carbon fibre layers. The hybrid laminates were found to have a flexural modulus of 3.25 GPa and Young's modulus of 3.66 GPa. Nevertheless, an attempt was undertaken to manufacture the prosthetic foot and socket with biocomposite materials. This chapter focuses on the discussion of prosthetic feet and sockets that are constructed utilising biocomposite materials. A comprehensive description of the mechanical characteristics of natural fibres and biocomposites is provided.

7.2 CLASSIFICATION OF NATURAL FIBRES

The classification of natural fibres typically consists of four categories: (a) plant, (b) animal, (c) mineral, and (d) advanced fibres, as seen in Figure 7.1. Natural fibres possess many characteristics, including elevated rigidity, reduced mass, increased

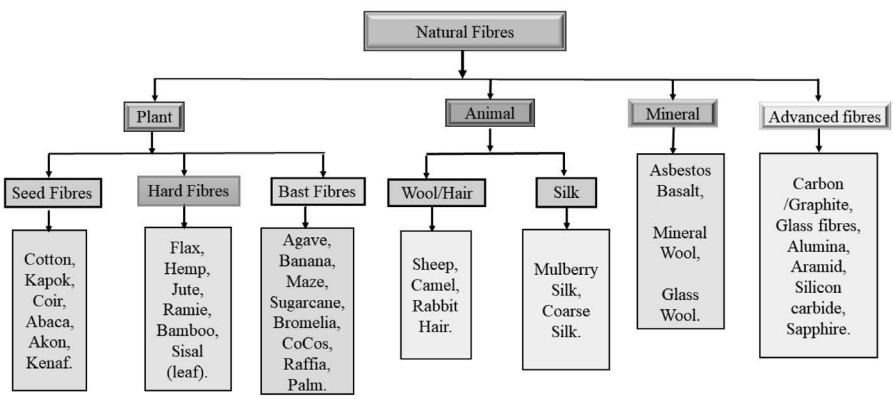

FIGURE 7.1 Classification of natural fibres.

disposability, renewability, improved mechanical qualities, and enhanced specific energy. Polylactic acid is a polymer that is now popular and may be used as a polymer matrix due to its biodegradability, non-toxicity, and eco-friendliness [17]. Over the last several decades, there has been a growing interest in enhancing the mechanical, biological, and thermal qualities of natural fibres (fibres derived from plants and animals) by reinforcing them with biodegradable polylactic acid polymers. The characteristics of NFPCs also differ according to the kind, source, and structure of the fibres. The chemical treatment of the natural fibres strengthened the adhesion between the surface of the fibres and the polymer matrix, hence improving the physicomechanical and thermochemical characteristics of the NFPCs. To decrease the moisture absorption of the NFPCs, the fibres may be subjected to surface modification techniques such as alkalisation and the incorporation of coupling agents [18, 19]. Plant-based fibres are highly suitable for biomedical applications due to their biocompatibility, similar strength to other fibres, and cost-effectiveness [20]. In the biomedical and bioengineering domains, natural fibres combined with bioresorbable polymers are used to create joints and bone fixings, which effectively relieve pain in patients. The biocomposites exhibited a significant improvement in mechanical characteristics, namely in terms of elastic modulus and ductility, when compared to the pure polymers. The mechanical properties of plant-based fibre composites generally improve with an increase in the fibre content within the polymer matrix. Table 7.1 provides information on the mechanical characteristics of several kinds of natural fibres.

TABLE 7.1
The Mechanical Properties of Natural Fibres (Plant and Animal Fibres)

Natural Fibres	Tensile Strength (MPa)	Elongation at Break (%)	Young's Modulus (GPa)	Flexural Strength (MPa)	Density (g/cm^3)
Flax [21]	345–1100	1.30–10.00	27.60	200–250	1.4
Jute [22]	394.00–773.00	1.5–1.8	13.00–26.50	60–80	1.48
Hemp [5]	550.0–900.0	1.6	30.0–70.0	45.0–80.0	1.48
Kenaf [22]	295.0–1191.0	3.5	53.0	19.43	–
Ramie [23]	384.0–938.0	1.2–8.0	44.0–128.0	25.30	1.5
Cotton [24]	264.0–800.0	7.0–8.0	5.50–12.60	–	1.5
Milkweed [25]	381.0	2.1	8.2	32.50	–
Coir [21]	131.0–175.0	15.0–25.0	4–6	29.226	1.2
Kapor [22]	90.0–95.0	1.8–4.2	4.0	–	–
Sisal [26]	500.0–800.0	2.0–25.0	9.40–22.00	29.28–62.50	1.34
Pineapple [25]	170.0–1627.0	2.4	65.0	80.20	1.4
Agave [27]	430.0–580.0	3.0–4.70	13.0	–	–
Banana [24]	529.0–914.0	3.0	27.0–32.0	57.33	1.35
Bamboo [24]	140.0–230.0	–	11.0–17.0	40.50	1.25
Silk [20]	650.0–750.0	18.0–20.0	16.0	24.0	–
Wool [5]	120.0–174.0	24.0–36.0	2.40–3.50	–	–
Corn	160.0–175.0	4.5–5.1	45.00	65.45	0.8

7.2.1 Cotton Fibres and Flax Fibres with Polymer

A novel method using vacuum moulding technology and adhering to the lamination pattern was used to fabricate the prosthesis socket, which consists of a mix of carbon fibres, perlon fibres, and flax fibres. Carbon fibres provide low weight and sufficient strength to withstand the load, while flax introduces an elongation factor that is both sustainable and environmentally beneficial. This combination has the potential to result in prosthetic devices that are both more comfortable and environmentally responsible, demonstrating the adaptability of three-dimensional (3D) printing and materials in the healthcare field. The prosthetic sockets consist of distinct layers, including four layers of flax fibres, three layers of cotton fibres, which have been treated with a 5% NaOH solution at room temperature, and two layers of carbon fibres, strengthened with polyvinyl alcohol (PVA). The prosthesis socket design incorporates four anatomical terms: anterior, posterior, lateral, and medial. These sockets are designed according to their ability to withstand weight and their analysis of motion. Von Mises stress and deformations are evaluated by applying boundary conditions at various points. Several investigations have shown that the deformations of prosthesis sockets would be minimal because of the high modulus of elasticity, indicating a high level of material stiffness [7]. Jweeg et al. [10] classify the deformations of the prosthetic sockets into three categories: lower, medium, and longer. It was determined that the overall deformation exhibited a proportionate relationship with length. Consequently, the total deformation of the medium socket was less than that of the long socket.

7.2.2 Sisal Fibres and Flax Fibres with Polymer

The prosthetic foot was fabricated using hybrid laminates composed of sisal fibres, flax fibres, and epoxy. The sisal fibres underwent treatment using solutions of NaOH and N-isopropyl-acrylamide. The chemical treatment leads to a decrease in both lignin concentration and fibre density, whereas the N-isopropyl-acrylamide treatment significantly reduces moisture absorption. The application of 2% N-isopropyl-acrylamide solutions to fibres resulted in improved tensile strength, compression strength, flexural strength, and impact strength compared to untreated fibres and those treated with NaOH solutions. TGA studies showed that the fibres exhibited enhanced heat resistance after the NaOH treatment. The pull-out experiments conducted on polyester resin demonstrated that all treatments successfully enhanced the interfacial adhesion [26, 28–32].

7.2.3 Jute Fibres/Pineapple Leaf Fibres with Polymer

Jute fibres are considered to be among the finest natural fibres due to their exceptional sustainability and lightweight nature. These natural fibres are used in the production of sockets for lower limb prostheses. Mishra et al. [33] used a jute fibre mat arranged bidirectionally with epoxy to create prosthetic sockets. The jute fibres' volume percentage was systematically altered from 0 to 48 wt.%, resulting in an observed increase in tensile strength from 43 to 110 MPa. The impact strength of epoxy composite materials

reinforced with jute fibres was determined to be 4.875 J at fibre content of 48 wt.%. The use of pineapple leaf fibres as a substitute for glass fibres in the construction of prosthetic limbs included the reinforcement of epoxy resin. The dimensions of the pineapple leaf must be tailored based on the individual's age and weight. Additionally, the price of pineapple leaf fibres is 50% lower than that of glass fibres [34–36]. Table 7.2 displays the mechanical characteristics of biocomposites reinforced with natural fibres.

TABLE 7.2
Mechanical Properties of Natural Fibres Reinforced Biocomposites

Composite Materials	Mechanical Properties	Remarks
Rattan fibres reinforced epoxy composites [12]	1. Flexural strength: 79.25 ± 4.0 MPa 2. Impact strength: 46.35 ± 0.70 kJ/m^2 3. Tensile strength: 65.30 ± 0.90 MPa 4. Compressive strength: 35.23 ± 0.40 MPa	Gait analysis of lower limb prosthesis socket by using a six-minute walk test (walking speed of 0.6 m/s and cadence of 86.3 steps/min).
Three layers of jute fibres and four layers of carbon fibres reinforced polyvinyl alcohol (PVA) [11]	1. Flexural strength: 261 MPa 2. Impact strength: 51 kJ/m^2 3. Shear strength: 16.35 MPa	The hybrid laminate of jute fibres and carbon fibres with PVA is used to obtain better strength and stiffness, along with being eco-friendly and cost-effective.
Hybrid laminate (three layers sisal, two layers carbon, and four perlon fibres layers reinforced with PVA [13]	1. Flexural strength: 225 MPa 2. Shear strength: 13.80 MPa 3. Impact strength: 80 MPa	The fracture toughness improves with growing layers and reaches its highest value of 24 MPam$^{1/2}$.
Carbon fibres and perlon fibres reinforced polyvinyl alcohol (PVA) bag [14]	1. Flexural strength: 66.70 ± 1.99 MPa 2. UTS strength: 95.066 ± 4.25 MPa 3. Young's modulus strength: 3.06 ± 0.3 GPa	Increasing carbon fibres up to 40.63% led to improve the magnitudes of ultimate tensile strength, which is comfort for the human body lower limb prosthesis.
Hybrid laminate of flax-sisal reinforced epoxy [15]	1. Tensile strength: 68.40 MPa 2. Flexural strength: 145.70 MPa 3. Compressive strength: 45.64 MPa	The prosthesis socket is made of treated flax fibres, jute fibres with 5% NaOH solutions, and epoxy. According to the researcher FEM analysis of the prosthesis socket is to be obtained with 2.214 MPa shear stress and 0.0064 mm deformations.
Transfemoral prosthesis socket made of jute fibre reinforcement with epoxy [16]	1. Tensile strength: 53 MPa 2. Impact strength: 47 kJ/m^2	This type of prosthesis socket reduces skin irritation, sweat, and improves pressure distribution during walking, and creates comfort while wearing the biocomposite sockets.

7.3 ADDITIVE MANUFACTURING TECHNIQUES

Additive manufacturing (AM) is a sophisticated process used to generate 3D components of prosthetic devices. AM, sometimes referred to as 3D printing, fast prototyping, or solid freeform fabrication, is a technology used to create objects by adding material layer by layer. The 3D-computer-aided design (CAD) model is used for the production of a 3D object. This object is divided into horizontal cross-sectional regions using electronic slices. This data is then passed to the AM machining process, where a 3D component is fabricated based on the 3D computer-added design model. The many kinds of AM methods include stereolithography (SLA), fused filament fabrications (FFFs), selective laser sintering (SLS), direct-write (DW), and polyjet printing (PP). These techniques are mostly used with polymeric materials, as seen in Figure 7.2. AM methods are used for both thermosetting and thermoplastic polymers. Thermosetting polymers, such as acrylics, epoxies, and acrylates, as well as thermoplastic polymers like polylactic acid (PLA) [37, 38], are within the scope of AM applications. AM is a method that uses step-by-step construction to create a 3D object from a computer-generated design inputted into a computer. The computer model is partitioned into horizontal strata, with one stratum subsequently constructed atop another [39]. The key benefit of AM is its ability to produce intricate components efficiently, using fewer stages and generating less material waste. Various types of AM procedures are available and are used for diverse products, based on factors such as the material, complexity, required qualities, and size. Presently, polymers are obtainable in several forms such as filaments, powder, resins, and reactive monomers. These forms are used by diverse AM methods to fabricate polymer matrix composites. The most often used AM methods for producing polymer matrix composites [40] are FFF, stereolithography (SLA), SLS, digital light processing (DLP), and binder jetting (BJ) procedures. Various AM processes have been used based on factors such as the kind

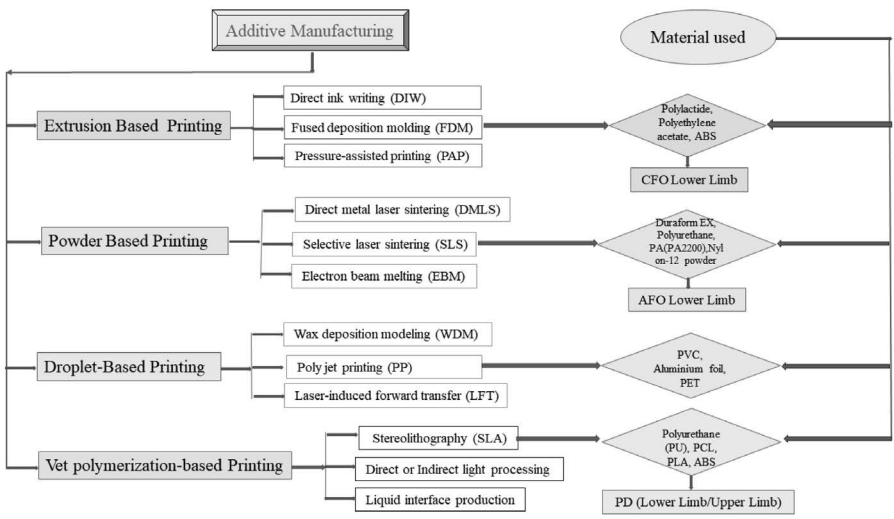

FIGURE 7.2 Schematic diagram for the classification of additive manufacturing technology.

of feedstock materials, the complexity of the component geometry, restrictions in processing precision, and the ability to deposit multiple materials [27].

7.3.1 Fused Filament Fabrications

The process referred to as fused deposition modelling (FDM) is used for the production of 3D objects. Polymer matrices may be reinforced with fibres in various orientations. The polymer composite pieces that were created demonstrated excellent dimensional accuracy and precision. Zein et al. [41] produced bioresorbable poly(ϵ-caprolactone) (PCL) scaffolds using FFF methods. PCL matrix materials, including polyethyleneimine (PEI), polycarbonate (PC), thermoplastic polyurethane (TPU), and polyether ether ketone (PEEK), are used in FFF to create porous scaffolds with varying compositions. The PCL scaffolds were manufactured using various processing settings, resulting in a variety of channel sizes (160–700 μm), filament diameters (260–370 μm), and porosities (48–77%). The scaffolds also exhibited regular honeycomb pores with geometric shapes. The compressive stiffness varied between 4 and 77 MPa, the yield strength ranged from 0.4 to 3.6 MPa, and the yield strain ranged from 4 to 28%. The tensile testing verified that the filled PLA filament exhibited superior performance in terms of both printing quality and thermomechanical properties. The primary drawback of this technique is its limitation to thermoplastic materials due to the undefined shrinkage limits of thermoplastics, which may lead to nozzle wear and clogging [42]. Porous polycaprolactone scaffolds were fabricated via FDM. The surface was covered with a layer of hyaluronic acid/β-tricalcium phosphate (HA/TCP). In vitro, the HA/TCP coating demonstrated enhancements in cellular proliferation, osteogenic differentiation, and homogeneous dispersion of the cellular matrix [43]. Figure 7.3 displays the schematic design of FDM.

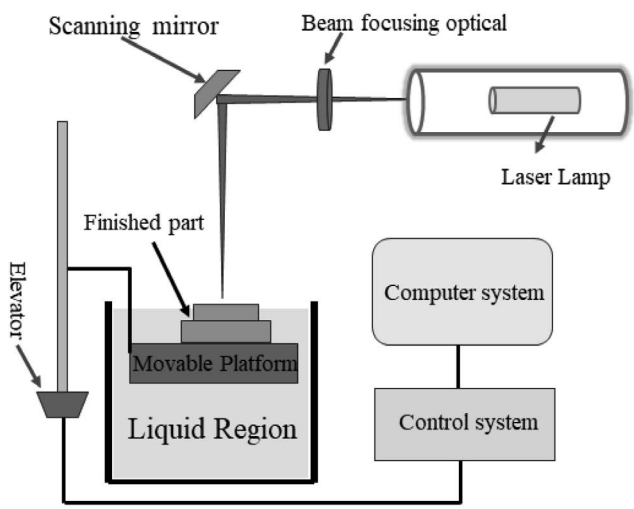

FIGURE 7.3 Schematic illustration of fused deposition modelling.

7.3.2 Stereolithography (SLA)

Stereolithography, similar to other solid freeform production methods, is an additive procedure that enables the creation of components from a CAD file. The planned external and internal (pore) shape of the structure that will be constructed can be created using 3D modelling software utilising mathematical equations [44] or obtained from scanning data generated by medical imaging technologies such as magnetic resonance imaging (MRI) or tomography techniques [45]. The use of data obtained from scans renders these manufacturing methods very advantageous for several applications in biomedical engineering, as it enables the production of models or implants tailored to individual patients. The CAD file provides a detailed representation of the shape and dimensions of the components that will be constructed. The development of the STL file format was intended for this purpose. An STL file contains a list of coordinates representing the triangles that together constitute the surface of the 3D object being constructed. The structure is divided into layers of a certain thickness, which is used in the layer-by-layer production process. Subsequently, the data is sent to the stereolithography equipment (SLA) for the purpose of printing the 3D structure. Figure 7.4 displays the schematic diagram of the stereolithography (SLA) technique.

7.3.3 Selective Laser Sintering

SLS is a contemporary 3D printing technique that utilises a laser beam to fuse powder particles together, resulting in the creation of solid objects (Figure 7.5). The medical industry is using this particular kind of 3D printing to create bioactive scaffolds. Typically, SLS is used to manufacture items with intricate shapes. Consequently, the elevation of liquid velocity in high-viscosity liquid with heated powder caused

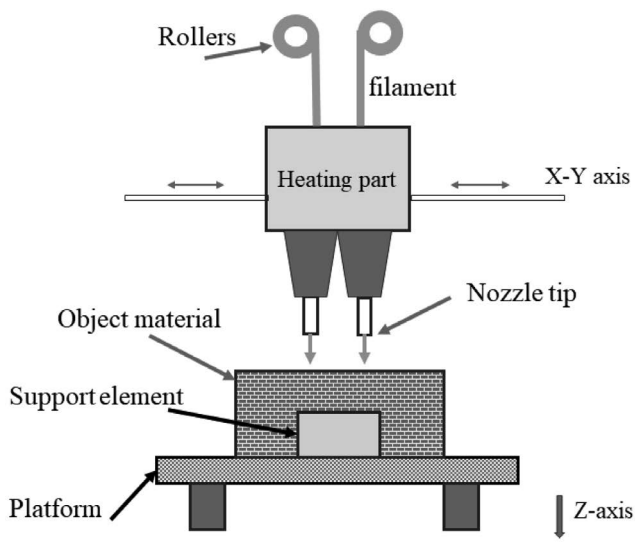

FIGURE 7.4 Schematic illustration of stereolithography process.

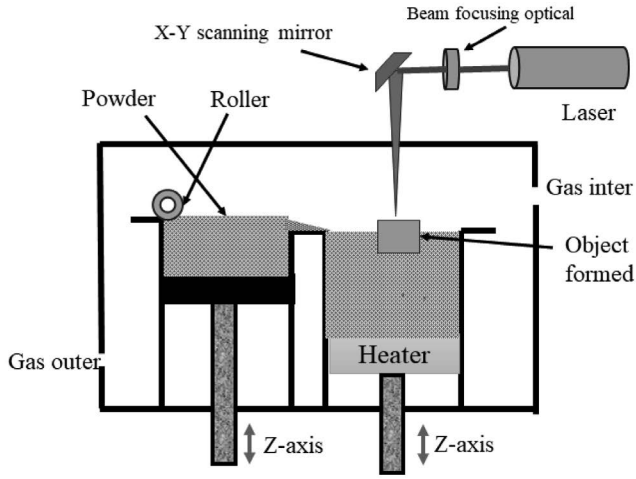

FIGURE 7.5 Schematic diagram of selective laser sintering (SLS).

harm to the specific region where the surface exhibits an orange peel-like texture [46–49]. Several biodegradable polymers, including polycaprolactone (PCL), polyamide, polyether ketone (PEK), and polyethylene (PE), have been effectively used both with and without reinforcement [50]. The drawbacks of this procedure include significant porosity in the printed component, costly processing, sluggish printing speed, and powder loss during processing [51].

7.4 BIODEGRADABLE POLYMERS

Biodegradable polymers are both ecologically and environmentally sustainable. The many environmental issues may be addressed by the use of renewable energy sources and the implementation of biodegradable matrix and fibres [52–54]. The prosthetic foot is fabricated using a biodegradable matrix material, as well as plant and animal fibres. When biodegradable polymer matrices are combined with natural fibres, the mechanical characteristics of polymer composites are enhanced owing to the strong cohesion forces between them [55]. The biodegradable polymer may be derived from many agricultural resources [56]. The many kinds of biodegradable polymers include polylactic acid (PLA), polycaprolactone (PCL), polyglycolide acid (PGA), and poly(p-dioxanone) (PDS), as mentioned in Table 7.3.

7.4.1 Polylactic Acid

Polylactic acid (PLA) is a biodegradable polymer derived from the synthesis of lactic acid. PLA is derived from renewable resources such as sugarcane, potatoes, starch, and maize grain [23]. Polylactic acid is used in the process of lactide production, which involves three stages: lactide formation, direct condensation, and dehydration condensation [24, 25]. PLA is used in a multitude of domestic applications, including plastic

TABLE 7.3
Mechanical Properties of Biodegradable Polymers

Biodegradable Polymers	Tensile Strength (MPa)	Yield Strength (MPa)	Elastic Modulus (MPa)	Flexural Strength (MPa)	Applications of Biodegradable Polymers
Polycaprolactone (PCL) [57]	25–43	9–11	330–360	12	Drug delivery for tissue engineering, surgical implant, bone tissue engineering, wound healing scaffolds.
Poly(lactic acid) (PLA) [58]	35	5–10	342	85.2	Suture, medical implant, screws and plates, haemodialysis, drug delivery, and used in textile applications, etc.
Poly(glycolide-acid) (PGA) [59]	110	–	–	70	Wound dressing, enzyme immobilisations, nanotechnology, surgical suture, tissue regenerations, drug delivery, and medical implants.
Poly(p-dioxanone) (PDS) [60]	80	–	110	–	Suture, implantable orthopaedic devices, clips, staples, etc.
Poly (hydroxy alkanoates) (PHA) [61]	185	–	60	–	Drug delivery and tissue engineering, hydrophilic castor, etc.
Polybutylene succinate (PBS) [21]	300	20–30	70	–	Surgical suture, tissue regenerations, drug delivery, etc.
Poly(butylene adipate-co-terephthalate) (PBAT) [22]	275	400	–	79	Mostly used for packaging, mulch film cutlery, etc.

bags, sanitary goods, cups, bottles, plates, and more. Poly(lactic acid) has exceptional strength, processability, and mechanical characteristics. PLA has superior tensile qualities compared to polystyrene PS and polyethylene terephthalate (PET). Poly(lactic acid) (PLA) is used in several sectors such as textile, plastic, packaging, and biomedical industries, namely in the production of suture threads and bone fixations. PLA has exceptional resilience and possesses a density of 1.24 g/m^3 [62]. Poly(lactic acid) (PLA) is used in the AM process. FDM is a technology used in AM. The FDM technique was used to fabricate the prosthetic foot utilising polylactic acid (PLA) material. This particular foot is referred to as an energy storage and returning foot [63, 64].

7.4.2 Polycaprolactone (PCL)

Polycaprolactone (PCL) is considered one of the most biodegradable polymers. PCL is a biodegradable polymer known for its exceptional flexibility. The film made from PCL has been shown to exhibit elongation and tensile strength at the break exceeding 100% at 35 MPa. Poly(caprolactone) (PCL) has been extensively used in the

construction of 3D scaffolds in the domain of bone tissue engineering, splinting, and modelling. The density of PCL is 1.145 g/cm^3.

7.5 CONCLUDING REMARKS

This chapter explores the latest advancements in the production of biodegradable prosthetic feet utilising AM techniques. The prosthetic foot was constructed using biocomposites composed of natural fibres and biodegradable polymers. Presently, biocomposites find use in several industrial areas such as housing, vehicles, infrastructure, and packaging. Various biodegradable polymers, including polylactic acid (PLA), polycaprolactone (PCL), polyglycolide acid (PGA), and poly(p-dioxanone) (PDS), are often used for lower limb prostheses using 3D AM methods. PLA and PCL are particularly preferred for this particular application. AM methods provide several benefits, including reduced time consumption, exceptional precision in creating composite components, and the ability to generate specified shapes.

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8 Technologies Assisting Additive Manufacturing in Biomedical

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8.1 INTRODUCTION

Contemporary markets demand heightened development and production standards, emphasizing product quality, flexibility, cost reduction, and rapidity in production cycles. Thus, a notable shift from mass production to personalized, small-scale manufacturing is observed in specific market segments. To cater to these evolving market needs, modern additive manufacturing (AM) processes have emerged since the late 1980s. AM is one such process characterized by layer-on-layer material addition, that facilitates intricate product geometry that conventional manufacturing techniques find challenging. AM remains a burgeoning technology with wide-ranging applications across various sectors like Bio-medical, aerospace, automobile, military, and fabrication industries, among others [1]. The medical sector has been significantly impacted by AM, particularly in the development of customized patient-specific implants, prosthetics, surgical instruments, and medical devices [2]. The innovative aspect of AM lies in its ability to effortlessly create highly intricate structures by building parts layer by layer, making it flexible for manufacturing challenging or complex parts that traditional subtractive techniques find difficult or impossible [3, 4].

The key advantage of 3D printing is its unique capability to manufacture exceedingly unfeasible parts to fabricate using traditional methods in a single run [5]. This encompasses hollow parts, structures with internal or porous configurations like tissues or cells for bioprinting, lattice-like scaffolds, dense internal networks resembling bones, and intricate geometries for dentures and organ printing. This versatility in both printing techniques and materials is a significant reason why 3D printing, although unconventional and relatively new, has found extensive applications in various domains, including medicine, healthcare, automobile, defense, and aircraft industries [6, 7].

This chapter comprehensively presents the current biomedical applications, bringing to light the transformative impact of 3D printing in areas such as dentistry, virtual surgical planning, customized surgical devices, tissue engineering, and bioprinting of living tissues and cells. A notable emphasis is placed on the plethora of printable materials suitable for 3D printing, ranging from plastic filaments like ABS, Nylon, PLA, and PET to metallic powder, ceramics, hydrogels, composites, carbon fiber, and biological cells [8]. This flexibility in printing methods and materials underscores the broad spectrum of applications 3D printing has in medicine, healthcare, as well as other industries.

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The chapter aims to underscore the rapidly expanding role of 3D printing in the biomedical, medical, and healthcare domains, highlighting its continuous growth and transformative potential. In the realm of 3D printing, bio-fabrication, or bio-printing, two distinct printing materials, namely, bioink and biomaterial ink, play a pivotal role [9, 10]. Hydrogel, known for its hydrophilic polymer chain network, stands out as a well-established printing material, forming the basis for numerous bioinks used in bioprinting, 3D cell culture, and regenerative medicines. These hydrogel-derived bioinks, including gelatin, alginate, silk, fibrin, cellulose, gellan gum, and agarose, are highly compatible with living cells, providing an aqueous 3D environment conducive to cell growth and proliferation, akin to the natural extracellular matrix (ECM) [11, 12].

8.2 WHY ADDITIVE MANUFACTURING IS A VITAL IN BIOMEDICALS

In recent times, a notable surge in demand for implants and scaffolds has become apparent, primarily driven by the escalation of road traffic accidents and issues related to human aging [13, 14]. Consequently, there has been a heightened imperative to fabricate patient-specific implants of exceedingly high quality to mitigate the necessity for repetitive surgeries, alleviate patient discomfort, and address the replacement of dysfunctional tissues [15, 16]. Conventional bone repair techniques such as distraction osteogenesis and bone grafts present inherent limitations [17]. Within this context, AM technologies have emerged as a highly viable option to produce diverse, flexible products with either a net or near-net geometry, using a layer-wise approach. Typically, patient-specific geometries are derived from magnetic resonance imaging or computed tomography scans. The merits associated with these products have notably reduced production time, mass customization, improved productivity, and minimal post-processing requirements [18]. Additionally, they also offer significant advantages including reduced surgical redundancy, enhanced implant stability, restoration of natural joint kinetics, facilitation of bone ingrowth, enhanced cell proliferation, commendable mechanical properties, and effective repair of osteochondral defects These biomedically fabricated items find widespread application in tissue as well as organ repair, drug delivery, clinical medicine, tissue engineering, and the development of patient-specific prosthetic implants [19]. Hence, it is arguable that AM holds substantial promise in the extensive spectrum of biomedical product manufacturing.

Biomaterials are widely utilized in various fields, and 3D printing has been applied in Orthopedics, dentistry, Medical Devices, prosthetics, and Surgical tools such as 3D-printed glass frames, lenses, hearing aids, among others. Moreover, it finds application in Virtual Surgical Planning, Drug delivery, and pharmaceutical utilities, involving 3D printing for implants, ingestible tablets, transdermal delivery, and tissue engineering encompassing 3D-printed organoids, 3D models, and implants. This chapter also discusses additional biomedical applications like 3D bioprinting of living tissues and cells [20], as well as the creation of personalized medical devices for complex deformities. There is a wide array of printable materials available, spanning from plastic filaments such as ABS (acrylonitrile-butadiene-styrene), nylon,

PLA (polylactic acid), PET (polyethylene terephthalate), and others, to diverse materials like ceramics, hydrogels, carbon fiber, composites, wood, rubber, biological cells, and more. This versatility in both the 3D printing method and the materials utilized is a key factor that enables 3D printing to have a multitude of applications across various industries, including Medicine, Healthcare, automotive, defense, and aerospace, despite it being a non-conventional and relatively recent manufacturing technology [21].

8.3 APPLIED AM TECHNOLOGY IN BIOMEDICAL

AM continues to thrive as a transformative technology with diverse applications across various sectors, including biomedical, aerospace, automobile, military, and fabrication industries [22]. In the realm of biomedical applications, AM has made remarkable strides, particularly in revolutionizing medical practices [23]. This transformation is evidenced by the ability of AM to fabricate tailored implants, prosthetics, surgical instruments, and medical devices designed to meet the unique needs of individual patients.

What sets 3D printing apart is its extraordinary capacity to create intricate structures effortlessly and employing a layer-wise approach. This allows the production of distinct or challenging parts that would otherwise be difficult or impossible to manufacture using conventional subtractive techniques [24]. Noteworthy biomedical applications include 3D bioprinting of living tissues and cells and the customization of medical devices to suit complex deformities [20], which extend to virtual surgical planning, enabling doctors to conduct virtual surgeries and plan for actual operations by printing vital body organs to a 1:1 scale [25, 26]. Tissue engineering applications include 3D-printed cartilage scaffolds made of ABS and PLA for tissue regeneration [27], as well as other materials like Ca_3SiO_5 cement scaffolds used for bone regeneration [28]. The chapter emphasizes the rapid growth of 3D printing in biomedical, and healthcare applications.

8.3.1 3D Bioprinting

Printing in 3D is widely used across diverse industrial and automotive sectors, but significant advancements have been particularly noted within the biomedical territory. Successful applications involve the creation of tissues, organs, implants, and drug modeling for pharmaceutical research. Notably, AM technology has played a pivotal role in the development of key biomedical products such as vascular stents for cardiovascular patients, and orthopedic implants [29]. Establishing a sustainable manufacturing system stands as the paramount objective of AM technologies, achieved through the reduction of energy consumption. The medical field uses a wide range of 3D printing methodologies, and some of the most prevalent categories of 3D printing employed in biomedical applications encompass stereolithography (SLA) [30], fused deposition modeling (FDM) [31], selective laser sintering [32], digital light processing (DLP), selective laser beam melting [33] electron beam melting (EBM) [34], binder jetting, and directed energy deposition [35]. Evaluating energy consumption in AM entails measuring both primary and secondary energy. The energy requirements

of all AM technologies are contingent upon their respective procedural needs [36]. Consequently, environmentally conscious production in AM necessitates minimizing energy consumption and mitigating detrimental emissions [37, 38].

Printing in 3D has the ability to fabricate parts in a single run, which has otherwise been exceedingly challenging using traditional manufacturing methods [39–41]. Within biomedical 3D printing, also known as bio-fabrication or bioprinting, two primary printing materials that take the spotlight are bioink and biomaterial ink.

Bioinks, notably hydrogels, form a hydrophilic polymer chain network. Hydrogels, recognized and extensively utilized, exhibit a remarkable affinity for living cells, making them a cornerstone in bioprinting, 3D cell culture, and regenerative medicine through cell encapsulation [42]. With distinctive properties such as non-Newtonian behavior and controlled stress relaxation, hydrogels lend themselves to nozzle and extrusion-based printing, emulating biological functions with precision [43]. Derived mainly from hydrogels, bioinks comprise hydrogel-based biomaterials like gelatin, alginate, silk, fibrin, cellulose, gellan gum, and agarose, offering exceptional water absorption capabilities and creating an aqueous 3D environment reminiscent of the natural ECM, pivotal for nurturing cell growth and proliferation [44]. On the other hand, biomaterial ink, a crucial printing material, distinguishes itself by its absence of cells and direct use in 3D printing applications such as scaffolds, bones, anatomical organs, or other body implants [45]. Beyond hydrogels and biomaterial inks, the biomedical 3D printing landscape encompasses a broad spectrum of biomaterials, including ceramics, resins, synthetic hydrogels, bone cement like Ca_3SiO_5, thermoplastics like ABS and PLA, and specialized porous filaments such as PORO-LAY and GEL-LAY utilized for 3D printed scaffolds [46].

8.3.1.1 Scaffolds

Bone possesses a natural regenerative capacity. However, in cases of substantial bone defects, normal healing becomes challenging and may progress to complex issues like tumors or trauma [47]. Traditional methods such as allografts, autografts, and artificial bone replacements using polymers and metals have been employed to repair bone defects. Scaffold preparation methods such as gas forming, freeze-drying, and phase separation have been utilized, but achieving precise control over pore size using these techniques proves difficult. Therefore, advanced techniques employing 3D printing have been introduced [48–50]. Scaffolds play a vital role in tissue repair and growth by replacing damaged or diseased tissues. Key properties of an effective scaffold include a porous structure, bioactivity, biocompatibility, and robust mechanical strength. These properties significantly influence cell attachment, viability, and proliferation [51, 52]. Among these properties, pore size stands out as a crucial factor influencing cell transport and organization [53]. The optimal pore size typically falls within the range of 100–700 μm [54]. A smaller pore size facilitates efficient nutrient flow through the scaffold [55, 56]. Leveraging 3D printing, it's possible to create scaffolds with controlled porosity and interconnectivity, enhancing their potential applications [57, 58]. Mechanical properties must align with neighboring tissues where the scaffold is placed to ensure appropriate stress shielding. Additionally, surface properties like wettability and roughness significantly

affect cell attachment, proliferation, and differentiation [59]. Various 3D printing techniques, including FDM, binder jetting, SLA, DLP, EBM, and powder sintering, can be employed for scaffold fabrication [60].

The process of bone regeneration hinges on the migration and recruitment of osteoprogenitor cells to the site of a defect, where they subsequently differentiate into osteoblasts, forming bone minerals like hydroxyapatite (HA) [61]. Strategies to augment the bioactive properties of scaffolds for bone tissue engineering involve using growth factors and facilitating gene deliveries. An ideal bone scaffold must comprise biocompatible materials, acting as a temporary support that can endure mechanical forces at the defect site until the host tissue achieves full recovery. Key requirements include a biodegradation rate akin to the bone formation process duration and an inter-connected porous structure essential for scaffold design [47, 62].

Synthetic biodegradable polymers like poly(glycolic acid) (PGA), poly(caprolactone) (PCL), and PLA, along with their copolymers, have garnered significant attention in the biomedical domain due to their ability to undergo degradation by hydrolysis through ester linkages, yielding non-toxic by-products [63, 64]. These polymers have been successfully employed in 3D printing to produce scaffolds for tissue engineering. For instance, Williams and coworkers achieved a PCL scaffold with physical properties similar to human trabecular bone using the SLS printing technique, enhancing its bioactivity by seeding bone morphogenetic protein-7 (BMP-7) [65]. The scaffold, mirroring a CT-scanned minipig condyle structure, demonstrated potential for producing patient-specific scaffolds. Calcium phosphate-based ceramics, closely resembling bone mineral in composition, have found extensive use as bone substitutes. Given their powdered form, the SLS method is often utilized to produce grid-like scaffold structures [66–68]. Additionally, 3D plotting is employed in conjunction with a post-sintering process, using binders and sacrificial polymers along with bioceramics to create printable inks [69].

Bone, a nanocomposite, primarily comprises HA (50–70%) and an organic matrix (20–40%), predominantly type I collagen [70, 71]. Collagen, a vital biomaterial, is extensively used in various tissue engineering applications due to its robust mechanical properties and biocompatibility. Inzana and colleagues showcased the 3D printing of a collagen and calcium phosphate composite for bone regeneration, implanting the scaffold in a murine femur with a critical defect size and confirming osteoconductivity. Additionally, 3D bioprinting has emerged as a recent biomaterial printing method, enabling the creation of 3D tissue constructs with cells embedded in hydrogels [72–74]. A multi-head bioprinting method, incorporating vascular endothelial growth factor (VEGF) and BMP-2 into various hydrogel blends with human dental pulp stem cells (hDPSCs) has been demonstrated. These hydrogels were 3D plotted onto a PCL scaffold framework, highlighting the potential to produce large-volume scaffolds, a significant challenge in tissue engineering [75, 76].

Cartilage, a tissue with limited natural regenerative capacity due to its avascular structure, necessitates strategic approaches for repair. The ECM of cartilage primarily comprises type II collagen and glycosaminoglycan, regulating chondrocyte phenotype expression and initiating chondrogenesis [77]. Unlike bone, cartilage needs to withstand load-bearing forces while providing low-friction surfaces, making it challenging to repair defects caused by osteoarthritis or high-impact injuries [78, 79].

Poly(ethylene glycol) terephthalate/poly(butylene terephthalate) (PEGT/PBT) block copolymer, 3D printed through the FDM technique, has enabled the fabrication of grid-like structured scaffolds for cartilage regeneration. The scaffold, seeded with bovine articular chondrocytes (bACs), exhibited mechanical properties akin to native articular cartilage while developing cartilage-like tissue in vivo [65, 80]. Researchers like Hung and coworkers have successfully 3D printed cartilage scaffolds using water as a printing ink solvent, allowing the incorporation of biomolecules with superior biocompatibility compared to inks requiring organic solvents. Another innovative approach involves the development of nanocellulose-alginate scaffolds using 3D bioprinting, demonstrating precision in creating grid, disc, human ear, and sheep meniscus constructs [81]. Moreover, the integration of 3D biological tissue and electronic components has been achieved, incorporating silver nanoparticles into alginate hydrogel to mimic human ears' structure [82]. Recent advancements involve the 3D printing of inorganic-organic hybrid scaffolds, showcasing promising elasticity, self-healing ability, and bioactivity, mimicking the compressive behavior of cartilage [83, 84].

8.3.1.2 Organ and Tissue Printing

Addressing tissue and organ failure arising from aging, diseases, accidents, or congenital defects stands as a pivotal medical challenge. The conventional strategy for combatting organ failure predominantly relies on transplants sourced either from living or deceased donors [20]. However, a persistent obstacle remains—the acute shortage of organs available for transplantation. For instance, in 2009, the United States faced a concerning situation: 154,324 patients were on the organ transplant waiting list, yet only 18% received transplants, and a tragic 25 individuals per day lost their lives while awaiting an organ [85, 86]. Beyond the scarce supply of organs, organ transplantation is a costly endeavor and involves the daunting task of locating a compatible donor. A promising avenue to alleviate this crisis lies within the realms of tissue engineering and regenerative medicine. Herein, the approach seeks to address the organ donor scarcity by harnessing the patient's own cells to construct replacement organs. This strategic move minimizes the risk of tissue rejection and the necessity to have a lifelong immunosuppressant regimen [23, 87].

Traditional tissue engineering traditionally involves the isolation of stem cells, their combination with growth factors, cultivation within laboratory settings, and seeding onto scaffolds to guide cell growth and differentiation into functional tissues. However, a significant leap in the field comes through the advent of 3D bioprinting, offering substantial advantages beyond the capabilities of traditional methods [88]. Bioprinting in 3D allows precise placement of cells and comprehensive digital control over a spectrum of parameters. This advanced technology entails layer-by-layer fabrication of cell-laden biomaterials, ultimately yielding 3D structures akin to human tissues. Among the materials of choice for scaffolds in this process, hydrogels often stand out, especially in the context of creating scaffolds for soft tissues owing to their desirable properties, including adequate strength and appropriate porosity [22, 87, 89].

Moreover, in 3D bioprinting, inkjet-based technology has gained prominence, being a prevalent method. It operates by depositing bioink, a concoction containing either living cells or biomaterials, onto a substrate, mirroring human tissues or organs in accordance with meticulously coded digital instructions. The technology

holds immense promise, and ongoing research continues to showcase proof of concept by successfully fabricating various body parts, including the knee meniscus, heart valves, spinal disks, cartilage, bones, and even artificial ears. Remarkably, biotechnological companies are actively investing in this sphere, exploring the vast potential for not only rapidly screening drugs but also potentially cultivating complete human organs for crucial medical research and groundbreaking advancements in drug discovery. The realm of healthcare is undoubtedly on the verge of a transformative era facilitated by the incredible prospects of 3D bioprinting [90, 91].

8.3.1.3 Disease Modeling

In the early phases of drug discovery and preclinical refining infectious disease models is crucial to minimize trial and error [92]. In one such situation, biofabrication seeks to produce biological systems by integrating cells, biomaterials, and biomolecules. This technology facilitates the creation of a specific living construct, leading to the development of an advanced in vitro model—essentially a miniature living tissue or organ that emulates physiological characteristics in an in vitro environment [93, 94]. When constructing advanced in vitro models, reverse engineering involves extracting critical data from living tissues, organs, or bodily systems to identify the fundamental design principles needed to replicate a new analogous structure [95]. Biofabrication plays a key role in this process, aiding in the creation of highly biomimetic structures with the desired arrangement of various cell types within an engineered context. These advanced *in vitro* models, unlike traditional *in vitro* cell cultures, have proven capable of mimicking both the physiology of natural tissues and the pathological traits of diseases. Moreover, they offer a valuable means of modeling diseases specific to species and predicting treatment responses using cell sources directly derived from the target species. All in all, advanced in vitro models boast greater similarity to native tissues and exhibit enhanced reproducibility compared to traditional in vitro and in vivo models [96]. Consequently, biofabricating these advanced in vitro models is anticipated to play a pivotal role in overcoming challenges associated with expediting candidate identification in the drug discovery process. In comparison to other biofabrication methods, 3D bioprinting stands out due to its unique approach of constructing layer by layer and selectively patterning various materials [97, 98]. Recently, there have been significant advancements in 3D bioprinting, utilizing cells as foundational units to directly build living tissues and organs from scratch. This breakthrough involves incorporating live cells into pre-gel solutions, effectively using them as bioinks to 3D print the specific tissue structures. As a result, 3D bioprinting has started to be applied in the creation of advanced in vitro models [29, 99, 100].

8.3.1.4 Stem Cell-Based Tissue Engineering

Tissue engineering is centered around delivering cell-based products to injured tissues or organs, aiming to restore their functionality. Within this realm, stem cells represent a potential game-changer due to their remarkable capacity for self-renewal and differentiation into diverse cellular types [101, 102]. Extensive research on stem cells has elucidated their anti-inflammatory, trophic, paracrine, and immunemodulatory functions, showcasing considerable therapeutic potential [103]. However, using stem cells alone has limitations in disease treatment. Combining stem cell and

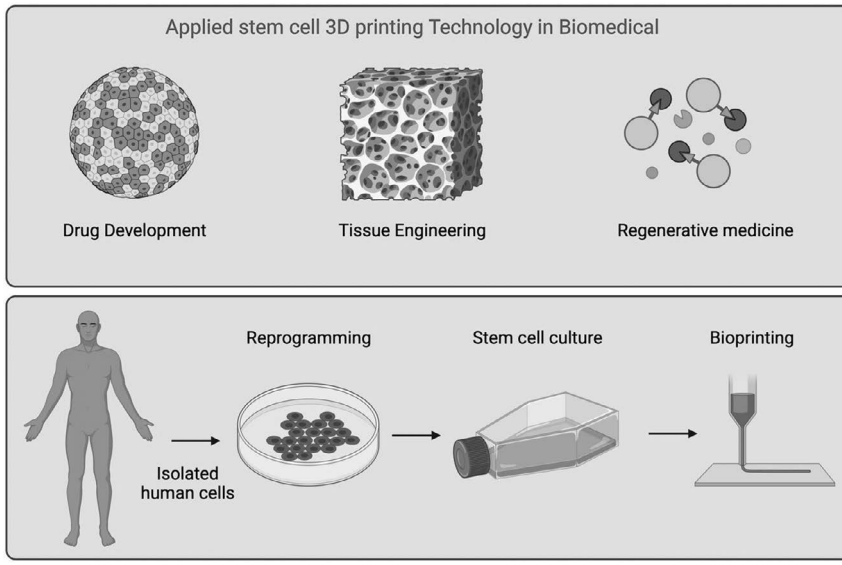

FIGURE 8.1 A descriptive view of 3D printing with stem cell technology.

tissue engineering techniques addresses these limitations, paving the way for functional substitutes in regenerative medicine as described in Figure 8.1. Although stem cells have a wide scope in disease treatment, their applied practices with 3D printing can be of significant mark in the field of biomedicine.

Induced pluripotent stem cells (iPSCs) hold a distinctive advantage in stem cell therapy and tissue engineering. Derived from adult somatic cells, they sidestep the ethical quandaries linked to embryonic stem cells (ESCs). Additionally, iPSCs can be easily sourced from superficial layers like skin fibroblasts, eliminating the need for invasive procedures like bone marrow or adipose tissue biopsies. iPSCs, being pluripotent, can differentiate into any adult cell type, augmenting their potential in modeling various disease processes. Their broad accessibility, being derived from diverse adult tissues, amplifies their source cell pool significantly compared to other stem cell types. Lastly, iPSCs can be transplanted in an autologous manner to mitigate immunogenicity and increase *in vivo* survival. Numerous studies have showcased the differentiation of human iPSCs into multiple lineages, including cardiomyocytes [104], neurons [105], hematopoietic progenitors [106], endothelial cells [107], osteoclasts [108], hepatocyte-like cells [109], and retinal cells [110]. Given these advantages, iPSCs hold promise for tissue engineering, cell therapy, and disease modeling.

Despite this expansive potential, technological hurdles persist in accurately replicating the intricate 3D structure of native tissues and organs in a hierarchical arrangement [111]. Achieving structural and functional mimicry akin to native tissues and organs is pivotal for successful tissue engineering [112]. A transformative technological platform that has emerged to address this challenge is 3D bioprinting, enabling precise deposition of diverse cells and biomaterials at predefined locations [113, 114]. Typically, these bioinks combine cells with biopolymer gels.

Recent exploration involves integrating iPSC technology with various 3D bioprinting approaches and strategies, aiming to engineer tissue and organ analogs with enhanced functionality for advanced regenerative medicine [115].

8.3.1.5 Virtual Surgical Planning

Another significant and widely recognized application of 3D printing in the field of surgery is the use of virtual surgical or operation planning. Advanced imaging technologies such as computed tomography scans enable the creation of highly accurate 3D replicas through high-resolution 3DP methods like SLA. These 3D printed models are invaluable for enhanced visualization and a more comprehensive understanding of anatomical parts or deformities before embarking on complex surgeries, a level of insight that would be challenging to attain through 2D imaging techniques alone [116]. Ultimately, these replicas are employed to strategize virtual surgery before the actual procedure. This virtual surgical planning proves essential for intricate cases involving deformities or injuries, such as pediatric deformities related to the spine, surgical bone realignment procedures, pelvic injuries, or deformities, among others [117].

8.3.2 4D Printing in Biomedicals

Printing in 4D represents an evolution in AM, integrating principles of 3D printing with materials capable of altering their shape, characteristics, or functionality in response to external cues as mentioned in Figure 8.2 [118]. The fourth dimension

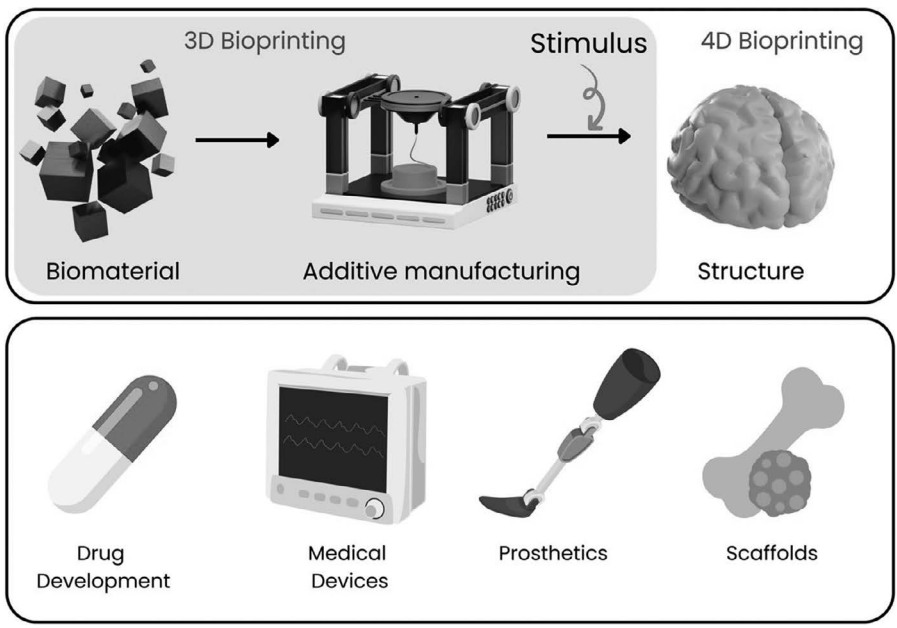

FIGURE 8.2 A point of differentiation between 3D and 4D printing technology along with their utility in biomedical.

signifies time, highlighting the dynamic behavior inherent in these printed structures. Utilizing materials responsive to stimuli, like shape-memory polymers, hydrogels, and bioinks, empowers the creation of dynamic structures capable of adapting to their surroundings, opening up novel avenues for biomedical applications [119].

In the intuition of biomedical engineering, 4D printing holds immense promise to revolutionize diverse facets of healthcare, spanning tissue engineering, drug delivery systems, medical devices, and diagnostics. The dynamic essence of 4D-printed structures allows the development of sophisticated and adaptable devices mirroring the intricate behavior of living systems, ultimately enhancing therapeutic results and enabling personalized treatments [120].

For instance, 4D printing can customize the engineering of products in the desired shape and configuration, thus promoting seamless integration with the adjacent tissue and stimulating cell growth and differentiation. Similarly, 4D printing can drive the creation of responsive systems that release their dose upon encountering physiological triggers, such as alterations in pH or temperature, ensuring more precise and controlled drug administration [120].

Furthermore, 4D printing also can enhance the performance of medical devices and prosthetics by enabling self-adjusting, self-assembling, or self-healing capabilities, thereby improving patient comfort, and achieving customized output. In diagnostics, 4D-printed devices adapt to varying biological conditions, delivering accuracy and dependability in detecting biomarkers, pathogens, or other analytes [121].

8.3.3 5D Printing for a Brighter Future

Although 3D and 4D printing has brought about a significant evolution in the medical arena, aiding in complex surgical procedures, pre-surgical planning, replacement of compromised bones, educational purposes, research, and training. However, the necessity for robustly curved implants within the human body has led to the introduction of five-dimensional (5D) printing in the medical sector, aimed at enhancing implant reliability and ensuring enduring strength [122].

Various engineering disciplines call for durable products that can endure prolonged usage, and 5D printing effortlessly meets this demand. This technique leverages a 5-axis technology to fabricate a 3D object, signifying the utilization of five axes in the printing process [123]. In 5D printing, the extra dimensions pertain to time and material characteristics. This implies that the printed object can undergo alterations over time or respond to diverse stimuli, like temperature shifts, humidity variations, or light exposure [124]. Precise regulation of printing parameters, such as temperature, pressure, and velocity, holds utmost importance to ensure the optimal viability and functionality of cells within the realm of 5D printing. Equally crucial is the utilization of bioink possessing specific attributes for applications in tissue engineering and regenerative medicine within the biomedical domain. Numerous materials, both natural and synthetic—such as hydrogels, alginate, collagen, gelatin, and fibrin—have been explored as potential bioinks. These materials can be tailored by incorporating bioactive molecules like peptides or growth factors, enhancing cell adhesion, growth, and differentiation [125].

It entails employing a 3D printer with five axes to fashion a more robust part compared to conventional 3D printing. During this process, the printing plate and head traverse along the X, Y, and Z axes, seamlessly generating a part with curved layers. The input data for this intricate process are derived from computer-aided design data. Moreover, this technology offers material conservation during the printing process and introduces a new dynamic range of motion for intricate structures, paving the way for innovation across manufacturing, medical applications, and various other domains.

On the other hand, 4D printing involves the utilization of self-assembling materials or smart materials to produce a 3D object. These materials possess the remarkable ability to alter their shape in response to changes in the human body's temperature over time [126, 127].

The limitations of traditional 3D printing in efficiently manufacturing components that meet these specifications underline the necessity for technological innovation to fulfill these critical requirements [122]. Experiments conducted to assess the strength of parts printed through 5D technology reveal their remarkable robustness, ranging from three to five times stronger than parts produced using conventional 3D printers. To illustrate, a cap crafted through 3D printing could withstand a pressure of only 0.1 MPa, while a cap produced using 5D printing could endure an impressive 3.7 MPa of pressure. Also, this significantly reduces material usage by approximately 25% compared to traditional 3D printing, efficiently prints curved parts with higher strength, and can produce objects larger than the print bed size in a single printing cycle. This technology fabricates robust products with intricate shapes without necessitating post-processing.

The creation of curved layers in 5D printing results in the fabrication of objects possessing markedly greater durability than those crafted using a 3D printer [125].

However, this technology is not without its limitations. The extra cost incurred due to the inclusion of two axes and the lack of awareness among the general populace regarding this transformative technology are noteworthy challenges. Operating and maintaining the customized machine necessitates skilled human resources and precise software and hardware.

Looking ahead, 5D printing holds immense promise for printing self-assembling materials with superior strength. It is poised to become an indispensable technology for printing intelligent curved medical components capable of adapting their shape over time. The technology is on track to find crucial applications in engineering, medicine, dentistry, and various other domains due to its proficient production of stronger parts in curved layers, making it a potent disruptive force in the medical realm. Consequently, 5D printing signifies a substantial leap forward in the medical sector, producing stronger 3D components in curved layers while minimizing material wastage.

8.4 FACTORS INFLUENCING PRODUCTION OF BIOMATERIALS USING AM

Designing biomaterials for bioprinting involves a range of important considerations, including the maturation process, matrix elements, cell composition, scaffolding, shape, and pattern, along with the mechanical dynamics of the printing equipment [128].

Biomaterials devoid of cellular components represent a fundamental building block in the development of non-living tissues such as bones. These biomaterials, essential for inkjet bioprinting, need to meet specific criteria: they must be non-toxic, biocompatible, and possess suitable rheological characteristics. Additionally, their viscosity is a critical factor, requiring it to be lower than in extrusion-based printing to ensure optimal flow and droplet formation [129]. Patterning, a pivotal aspect in biomaterial production, plays a crucial role in dictating the biological performance and functionality of the end products from the very beginning, unlike bioinks and other living materials that can adapt and evolve. The lack of living cells in biomaterials necessitates them to function flawlessly right from the manufacturing stage [130, 131].

When producing biomaterials, another crucial consideration is porosity, with macro-scale architecture significantly influencing biological performance and determining product functionality. Patterning during scaffolding introduces vital geometrical cues, encompassing the surface, topography, shape, size, and tortuosity of the porous elements. These factors are significantly influenced by the dimensional scale of production [73]. Various methods have been reported to achieve this, as demonstrated by Zhang et al., showcasing the micro-patterning of PCL scaffolds with a groove through a combination of electrospinning and micro-molding [132]. The outcomes revealed a micro-porous complex structure with heightened hydrophobicity and mechanical properties in the micro-patterned PCL scaffolds. Notably, this patterned microstructure of PCL displayed enhanced regulation of Schwann cell attachment without compromising the normal biological function within the cells. Furthermore, to enhance the attachment and growth of natural cells on a biomaterial, patterning is employed to facilitate better adhesion and growth of polymers by the body's natural tissues. Moreover, patterning during the printing process can be utilized to align micro-scale elements.

Next vital yet recurrent component in bioprinting is Bioink, which encapsulates cells or cell clusters within a biomaterial matrix, allowing for the precise construction of intricate structures [10]. It's broadly categorized into four types: support, structural, fugitive, and functional bioinks, each tailored to specific needs. A stellar bioink must meet three key criteria: ensuring cell viability during the printing process, aligning mechanically with the chosen printing technique, and directing cell behavior for optimal tissue regeneration [133]. Strategies focusing on vascularization stabilization are being explored to enhance cell viability during bioprinting, particularly critical for thicker structures. The concentration and composition of the bioink significantly affect cell survival rates, showcasing the nuanced nature of this essential bioprinting element. Through meticulous selection and fine-tuning, bioinks play a pivotal role in pushing the boundaries of 3D bioprinting, enabling groundbreaking advances in regenerative medicine and tissue engineering [134]. Within these, Hydrogel-based bioinks represent a prevalent choice for bioprinting, characterized by their ability to create a well-hydrated environment conducive to cellular processes. These hydrogels offer adaptability, allowing for easy modification to incorporate bioactive molecules that guide cell behavior and mechanobiology [135]. However, their rapid degradation poses a challenge, potentially inducing adverse effects on cells, particularly with synthetic gels due to acidic by-products

from polyester chains and ester bonds. Addressing this, Boere et al. [136] proposed integrating thermo-responsive polymers with cross-linkers like PEG or hyaluronic, effectively enhancing mechanical properties and impeding degradation, a method substantiated by Camci-Unal et al. [137].

Incorporating nanoparticles, adopting double-network, or double-crosslinking techniques in natural biomaterials like hydrogels becomes pivotal to bolster their mechanical properties, compensating for the inherent lack of strength during bioink processing. This strategic augmentation ensures enhanced chemical stability and customizable swelling characteristics. Furthermore, blending HA with methylcellulose, poly(glycidol)s (P(AGE-co-G)), and alginate amplifies their mechanical attributes. However, careful consideration of biocompatibility and toxicity is essential when incorporating fillers into natural biomaterials, emphasizing a cautious approach to maintain suitability for specific applications, such as wound dressing, while ensuring compatibility with living systems.

Additionally, 4D bioprinting has been seamlessly integrating the dimension of time into the conventional 3D printing process, particularly focusing on hydrogels [138, 139]. Unlike the static view of the initial state seen in traditional 3D printing, 4D bioprinting acknowledges that biomaterials and living cellular constructs evolve over time after the initial printing. This introduces a profound shift, addressing a significant limitation in current 3D bioprinting and propelling the field into a new dimension. Bioprinting in 4D harnesses the potential of responsive biomaterials and AM, culminating in the creation of structures that can self-assemble and dynamically adapt, offering innovative solutions in medical regeneration, especially where time plays a critical role, such as in tissue regeneration.

8.5 RESTRAINTS AND FUTURE PROSPECTS IN ADDITIVE MANUFACTURING

Printing in 3D and AM (3DP/AM) has emerged as transformative technologies, fundamentally altering traditional product lifecycles and challenging established business models [140]. The extensive adoption of 3DP across industrial, medical, military, automotive, aerospace, and various other sectors has the potential to disrupt existing structures. The societal implications of 3DP encompass factors like work quality, work intensity, evolving employment models, job displacements, and the demand for acquiring new skill sets. Studies also indicate that 3DP contributes to societal well-being through improved life expectancy, population health, and enhanced overall quality of life [141].

In the domain of medicine, healthcare, and bioprinting, there exist certain constraints. While bioprinting and careful bioink selection can create a conducive growth environment for tissues or cells, a dilemma arises concerning the bioink's structural support for the 3D printed model [142]. Opting for a bioink that prioritizes structural support may compromise cellular viability. Thus, a delicate balance must be struck between these two functionalities. Biomaterials with heightened elasticity facilitate the printing of intricate models that retain their form but limit cellular mobility and interaction. On the other hand, viscous biomaterials enhance cellular movement and

interaction but hinder the creation of complex, large models that can withstand their own weight without collapsing. As the realm of 3DP in healthcare, medicine, and bioprinting advances, the critical need arises for the discovery of novel biomaterials that seamlessly integrate structural support and cellular viability, eliminating the necessity for compromising either functionality [131]. The advancement of 4D printing in biomedical applications is remarkable, yet substantial challenges persist, hindering its widespread adoption in clinical settings. A critical concern is the limitations in materials, particularly in terms of properties and biocompatibility. Smart materials like shape-memory polymers and hydrogels must exhibit specific responses to stimuli yet finding the ideal materials with the requisite mechanical properties proves challenging. Biocompatibility is paramount but often restricts material choices. Addressing these challenges necessitates novel biomaterial development, potentially through composite materials, meticulous process parameter optimization, and a deep understanding of material-process-application interplay. Fabrication complexities, encompassing integration of multiple materials, resolution, accuracy, and scalability, pose additional hurdles. Achieving high resolution and scalability in 4D printing, while maintaining regulatory compliance and ethical considerations, demands focused research, multidisciplinary collaboration, and tailored strategies for each biomedical application, underscoring the need for a holistic and meticulous approach to unlock the full potential of 4D printing in biomedical engineering [143].

As AM progresses, the cost of hardware is expected to decrease, and the discovery of novel biomaterials and bioinks will significantly propel advancements in tissue engineering and regeneration applications. Commonplaces are thermoplastic components produced by affordable 3D printers, extensively utilized in hospitals and research institutions due to their versatility. Bioprinting has emerged as a potent tool for crafting intricate 3D structures resembling anatomical systems, crucial for disease modeling, drug testing, and screening. The technique has successfully generated foundational functional units of anatomical organs, referred to as organoids. However, the ultimate triumph of bioprinting lies in achieving the potential to 3D print fully functional organs for direct transplantation into patients. Overcoming limitations like micro-vascularization and developing unique, long-lasting bioinks is essential for realizing this milestone. Given the transformative impact of 3D printing on biomedicine and healthcare and its rapid evolution, it is reasonable to anticipate that bioprinting will soon reach its zenith, enabling the fabrication of fully functional organs.

8.6 CONCLUSION

This chapter discusses the contemporary claim of AM in the medical and healthcare sectors, highlighting its advantages over traditional manufacturing methods and underscoring the need for exploring novel biomaterials. Bioprinting has emerged as a valuable tool for generating 3D tissue-like structures mimicking anatomical systems, crucial for disease modeling, drug screening, and testing. The technique has successfully fabricated fundamental functional units of anatomical organs, building scaffolds, implants, tissue fillers, targeted drug delivery, and regenerative medicine. Considering the revolutionary impact of 3D printing on the field of biomedicine and healthcare, coupled with its rapid advancements, it is

plausible to anticipate that bioprinting will fulfill its potential and fabricate fully operational organs in the foreseeable future. Along with the tremendous developments made by 3D technology, 4D and 5D bioprinting have been equally ascending to the peak. However, to achieve this milestone, bioprinting must address limitations such as micro-vascularization and the development of unique bioinks with extended viability. As AM continues to progress, the cost of hardware is anticipated to decrease, and the discovery of new biomaterials and bioinks will further propel tissue engineering and regenerative applications. Conclusively, the evolution of AM has remained quite impressive, which is anticipated to create a revolution in the field of biomedical.

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9 Insights of Additive Manufacturing Technology for Biomedical Applications

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9.1 INTRODUCTION TO ADDITIVE MANUFACTURING IN BIOMEDICAL APPLICATIONS

Additive manufacturing (AM) is a process for creating three-dimensional (3D) components by building them up layer-by-layer from a computer-aided design (CAD) file. According to the International Organization for Standardization (ISO) [1], seven broad categories are defined for AM processes: material extrusion, vat photopolymerization, powder bed fusion, material jetting, binder jetting, sheet lamination, and directed energy deposition. All these technologies are well-established with processes and materials and are widely used in various sectors. Various features of these processes are illustrated in Table 9.1.

AM is now becoming a disruptive technology in various industries as it allows users to build complex geometries, customized parts with reduced waste, and most importantly, without using an intermediate tool. This process gained popularity in the late 1980s, and the evolution of this process has taken place from manufacturing prototype parts to direct functional components. The adoption of this technology has also evolved over time, and now, across all the fields, AM is exhaustively being used. The medical industry is one of the major sectors where AM allows the manufacturing of customized prosthetics and implants tailored to individual patient anatomies. Tools and models for surgeries become easier with the flexibility in design. Bioprinting is the latest research in AM, where tissues, bones, and organs can be printed with design optimization.

The medical industry started utilizing AM in the early 1990s with its first implementation in dental applications; however, with advancement in high-resolution imaging data for 3D models with Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans, the utilization of AM gained a higher momentum in the 2000s. AM has now established itself as a highly effective tool in the biomedical field, offering significant technical advantages. Through careful implementation, AM reduces the number of production steps required for manufacturing medical components, minimizes material waste, decreases inventory requirements, and removes the

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TABLE 9.1
Seven Categories of Additive Manufacturing and Their Features

Sl. No.	Process	Features	References
1	Material extrusion	• Material is extruded through a nozzle or orifice • *Process*: Fused Deposition Modeling (FDM) and Fused Filament Fabrication (FFF) • Support material may be required, cost-effective, used for prototypes and functional parts • *Materials*: Thermoplastics, metal pastes, and composites	[2–4]
2	Vat photopolymerization	• Curing-based process by a light source • *Process*: Stereolithography (SLA) and Digital Light Processing (DLP) • Very high precision, good surface finish, preferred for small features • *Material*: Photopolymers	[5, 6]
3	Powder bed fusion	• Laser or electron beam are used for fusing powder material • *Process*: Selective Laser Sintering (SLS), Direct Metal Laser Sintering (DMLS), and Electron Beam Melting (EBM) • Costly, high strength in component, preferred for functional parts • *Materials*: Metals, polymers, ceramics	[7–9]
4	Material jetting	• Droplets on demand, curing-based process • *Process*: Polyjet/multijet printing • Multi-material, color product, suitable for prototype • *Materials*: Photopolymer and waxes	[10, 11]
5	Binder jetting	• Liquid binder is deposited on the powder bed • *Process*: Material-based customization, popular as binder jetting • Large components, complex geometries, user can select powder and a suitable binder • *Materials*: Any material with a suitable binder	[11–14]
6	Sheet lamination	• Sheets are adhered using glue or heat, cut and paste or paste and cut technique • *Process*: Laminated Object Manufacturing (LOM) • Large component size, material waste is high, not suitable for complex features, generally for prototype or pattern making • *Material*: Paper, metal, or polymer (all in sheets)	[15]
7	Directed energy deposition	• High-intensity thermal energy (arc/laser/plasma/electron beam) are used to melt the material (in wire or powder form) • *Process*: Laser Engineered Net Shaping (LENS), Wire Arc Additive Manufacturing (WAAM), Electron Beam Additive Manufacturing (EBAM) • High deposition rate, typically all weldable material, high strength, for direct functional parts, used for repairing local damage • *Materials*: Mostly for metals, limited for polymers	[16–20]

necessity for extensive tooling [21, 22]. This technology also enables the full production of complex parts in a shorter time frame and at a lower cost, optimizing both efficiency and resource utilization in medical manufacturing [22, 23]. Over the decade, it has been observed that AM has become more demanding in the medical industry due to the following factors.

i. *Customizability*: Personalized medical devices and implants can be fabricated using patient-specific anatomical data, enhancing comfort, fit, and overall effectiveness.
ii. Rapid production without intermediate tooling.
iii. Creation of complex and porous structures with less risk of rejection.

Generally, these facilities in the medical industry are limited to conventional manufacturing processes.

9.2 COMPARISON OF ADDITIVE AND CONVENTIONAL MANUFACTURING IN BIOMEDICAL APPLICATIONS

Conventional manufacturing processes in the medical industry typically require multiple stages, each involving specific tooling to achieve the final product. Methods such as milling, casting, and molding are commonly used, but these processes tend to be both time-intensive and costly due to the extensive setup and labor required for each step.

For large-scale batch production, these conventional methods remain cost-effective because economies of scale can offset the initial tooling and production costs. However, in the medical field, production volumes are generally limited because devices and components are often customized for individual patients or made in small batches. This low production volume reduces the economic advantage of conventional manufacturing methods, as the high fixed costs for tooling and setup are not easily amortized across large quantities, making AM increasingly attractive for medical applications. AM reduces tooling requirements and allows for direct production from digital designs, streamlining the process and enhancing cost-efficiency for low-volume, customized medical parts.

AM offers significant advantages over conventional manufacturing, particularly for biomedical applications. Its layer-by-layer construction allows for faster production, reducing lead times and eliminating the need for costly tooling. AM is highly material-efficient, as it uses only the necessary amount, minimizing waste—a critical benefit for costly, biocompatible materials used in medical devices. Moreover, AM supports intricate and complex designs that are difficult to achieve with traditional methods, allowing for custom, patient-specific devices that enhance fit and functionality. It also enables rapid prototyping, facilitating quick design iterations and innovation. These features make AM more cost-effective for low-volume, customized production, positioning it as an ideal choice for the biomedical industry. A comparison of AM versus conventional manufacturing for biomedical applications is presented in Table 9.2.

TABLE 9.2
Comparison of Additive versus Conventional Manufacturing in Biomedical Applications

Factors	Additive Manufacturing	Conventional Manufacturing
Manufacturing process	Uses layer-by-layer manufacturing approach from a digital model	Uses subtractive, casting, or forming approaches to build the components
Customizability	High	Low
Complex geometries	Complex and porous structures are possible	Possible and often difficult and adds cost to achieve
Material efficiency	Very high as the required materials are only deposited with minimal waste	Very less as material removal is too high in subtractive process
Quality consistency	Depends on quality of every individual layer, usually low	Highly consistent in quality
Application versatility	Highly flexible	Very limited
Material options	Limited but not restricted (research ongoing)	Established and standardized
Production time	Relatively short time as it manufactures directly from digital file	Relatively long time as it involves tool preparation time
Cost	Cost-effective for low-volume, custom parts (e.g. implants)	Economical for high-volume but inefficient for custom parts

9.3 MATERIALS USED IN ADDITIVE MANUFACTURING FOR BIOMEDICAL APPLICATIONS

AM encompasses various processes, each utilizing distinct forms of materials, and the range of materials compatible with AM techniques is continually expanding. For biomedical applications, the selection of materials remains somewhat limited due to stringent biocompatibility and performance requirements. However, ongoing research is expected to broaden the material options suitable for AM in the biomedical field. Table 9.3 presents some of the most commonly used materials currently employed in biomedical AM applications.

TABLE 9.3
Materials Used in Additive Manufacturing for Biomedical Applications [21, 24]

Sl. No.	Material	Description
1	Acrylonitrile butadiene styrene (ABS)	• High rigidity, dimensional stability • Used for manufacturing insulin pens and inhalers
2	Polylactic acid (PLA)	• High strength • Biocompatible • used in tissue engineering, biodegradable fixation pins, screws

(Continued)

TABLE 9.3 *(Continued)*
Materials Used in Additive Manufacturing for Biomedical Applications [21, 24]

Sl. No.	Material	Description
3	Polyvinyl alcohol plastic (PVA)	• used for manufacturing pellets, sheets, sponges, foam, microspheres
4	Tissue and cell	• Used for improving whole organ/damaged tissue, creating new cell type
5	Polyurethane foam	• Used for manufacturing scaffolding implants, medical devices, surgical drapes
6	Graphene	• High strength, abrasion, biocompatibility • Applicable in cancer treatment applications, used for implants, coating stents for safe surgery
7	Titanium	• Biocompatible, non-allergic, lightweight, and strong • Used for manufacturing hip implants, bone screw, heart valves, and dentistry part
8	Magnesium	• Biocompatibility, anti-bacterial property, lightweight • Biodegradable implants, prosthetics
9	Nitinol	• High elasticity • Used for medical implants
10	Polyethylene	• Manufacturing implants for knee and hip replacement
11	Silicone	• Used for medical implants like tracheal stents • Reusable diagnostic and surgical tools
12	Polyether ether ketone (PEEK)	• Lightweight, good biocompatibility, and mechanical strength • Used for manufacturing medical tubing, bone screws, and pins, orthopedic, dental, and spinal implants, heart valves and stents
13	Alumide	• High strength • Used for hearing aids and prosthetic hands
14	Carbon fiber	• High strength • Coating of plastic parts • Used for manufacturing patient's lost limb

9.4 APPLICATIONS OF ADDITIVE MANUFACTURING IN BIOMEDICAL FIELDS

AM has been employed in a variety of biomedical applications, including the development of tissue engineering scaffolds [25], and the production of personalized prosthetics [26, 27]. One of the major biomedical applications of AM is the freedom to create patient-specific implants and prosthetics on a case-to-case basis.

Researchers, clinical practitioners, and healthcare providers can make dental implants and devices, orthopedic implants, and prosthetic appendages that are customized to the unique anatomy and needs of each patient regardless of the clinical variation [28]. These techniques prove to be better for the adaptation of prosthetics or implants within the body as the geometries can be altered strategically to provide better comfort and reduced recovery duration.

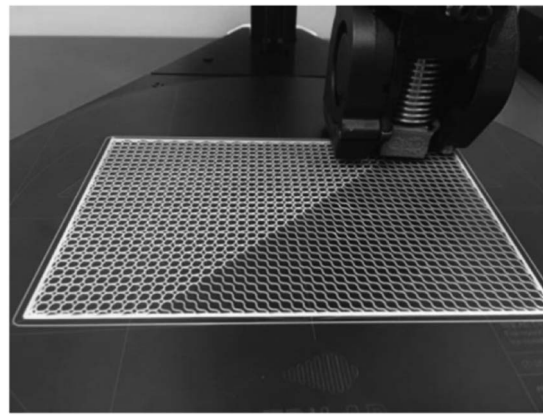

FIGURE 9.1 3D-printed scaffolds [29].

One of the case studies highlighting 3D-printed scaffolds, as shown in Figure 9.1, was presented by Balogová et al. [29], which focused on the treatment of subjects with infected skin regions. In this study, the affected region was treated with 3D-printed scaffolds, which aid in natural healing and skin regrowth.

Tissue engineering has also proven to be a promising technique using AM. Researchers have used this technology to create scaffolds that mimic the intricate architecture of natural tissues, such as bone, cartilage, and vascular structures, which can vary in size, structure, or composition. These scaffolds can be reconfigured to include different types of cells, growth factors, and other biomolecules. These scaffolds can be impregnated with specific drugs that are released over time in specifically targeted regions, which creates an environment that helps cells grow and differentiate, which leads to the regeneration of healthy tissues [25, 30].

As an alternative to traditional plaster cast, it may be beneficial to examine the case study that concentrates on 3D-printed splints constructed from PLA and PLA-$CaCO_3$ composites [31]. This example emphasizes a more cost-effective and accessible implementation of AM for the management of bone fractures. The advantages of these prostheses over traditional plaster casts include enhanced comfort, hygiene, and water resistance.

Another study by Nwankwo et al. [28] utilizes a 3D-printed titanium cage to address traumatic distal tibia segmental bone loss and multiple foot fractures. The implant was designed with the patient's specific anatomy and injury site, resulting in a more precise fit and improved integration with the adjacent bone. The use of a 3D-printed titanium cage in the treatment serves as a case study that highlights the potential of AM in biomedical applications. The customized implant successfully stabilized the patient's limb, leading to improved functional outcomes and limb salvage. This study was carried out with a five-year follow-up post-op, which resulted in a complete recovery of the patient with remarkable bone regeneration [28].

Through AM, researchers can generate scaffold structures that are both intricate and highly porous, emulating the natural extracellular matrix. This environment is conducive to cell adhesion, proliferation, and differentiation [27].

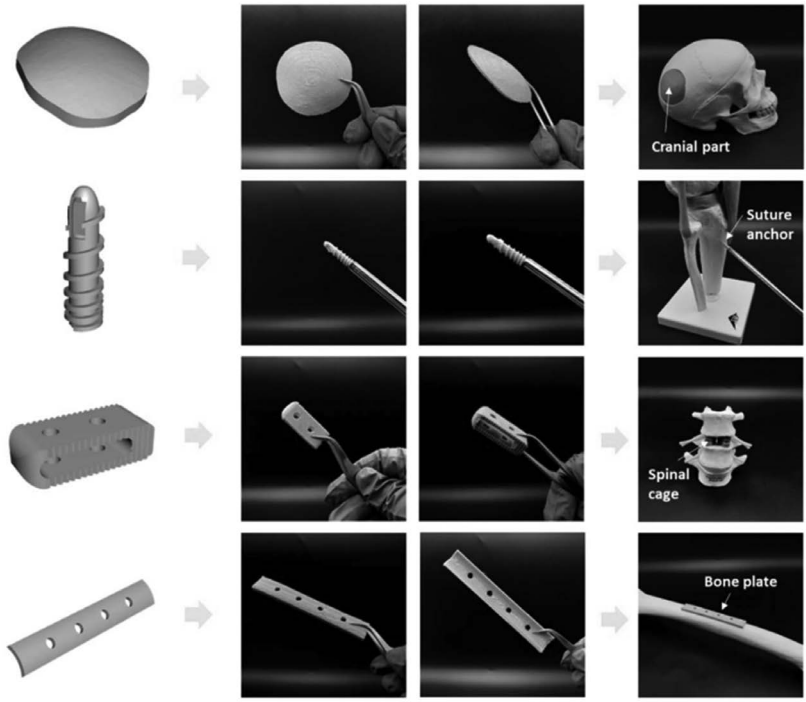

FIGURE 9.2 Bone implants and braces are bio-fabricated using AM techniques [32].

Some of the commonly used implants and supports manufactured by AM techniques are illustrated in Figure 9.2. These include maxillofacial implants of missing pieces of the cranium due to birth defects or injury, titanium suture anchors that are used in ligament reconstruction procedures, spinal cages that are used in patients with slip-disc in the spine, and orthopedic plates (mentioned sequentially top to bottom, as shown in the image).

In another application under prosthetics [33], a 3D-printed human ear manufactured with biocompatible material is operated on a human, and an illustration of pre- and post-operative conditions is depicted in Figure 9.3.

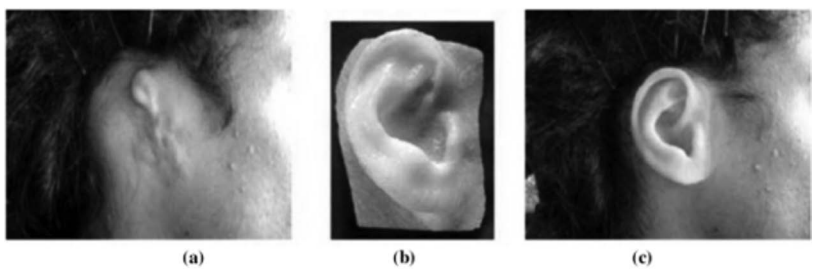

FIGURE 9.3 (a) Pre-operative patient situation, (b) 3D-printed human ear, (c) post-operative patient situation [33].

These developments in AM have created novel opportunities for regenerative medicine, enabling the creation of personalized tissue and organ replacements which utilize cells from the patient's body as the growth factor, which have better adaptation with the body of the patient and hence reducing the occurrence of organ or tissue rejection and similar complications [34, 35]. Healthcare providers can generate patient-specific implants and prosthetics that are precisely tailored to the individual's anatomy by employing 3D scanning and CAD software. This technology has been particularly advantageous in the treatment of intricate bone and joint injuries, where conventional off-the-shelf implants may not be compatible with the patient's distinctive anatomical characteristics due to clinical variations, age, or genetic conditions [25, 29, 30, 36–41].

9.5 CHALLENGES AND LIMITATIONS IN BIOMEDICAL ADDITIVE MANUFACTURING

Although AM has demonstrated significant potential in the biomedical sector, there are numerous obstacles and constraints that must be resolved. The biocompatibility and in vivo reliability of the materials employed in AM are among the most significant obstacles. Polymers and metals, which are frequently employed in 3D printing, may not have the requisite biocompatibility or bioreactivity to facilitate tissue integration and cell growth. In order to address this issue, researchers are investigating the utilization of biomaterials, including hydrogels and biocompatible composites, which can more closely resemble the natural extracellular matrix and facilitate cellular activities [37].

Other constraints include the reproducibility and scalability of AM processes for large-scale production. The mass production of medical devices or tissue-engineered constructs may be restricted by the inability of current 3D printing technologies to generate large or complex structures at a high volume.

9.6 FUTURE TRENDS IN ADDITIVE MANUFACTURING FOR BIOMEDICAL APPLICATIONS

Researchers and clinicians are investigating novel and thrilling opportunities for its implementation in the biomedical sector as AM technology continues to develop. An emerging trend is the integration of AM with other advanced technologies, including bioprinting and organ-on-a-chip platforms.

Bioprinting, which involves the use of 3D printing to generate biological tissue structures, has the potential to revolutionize regenerative medicine and tissue engineering. Researchers can create intricate, functional tissue constructs that can be employed for disease modeling, drug testing, and ultimately, organ transplantation by integrating bioprinting and AM.

The development of multifunctional AM systems that can seamlessly incorporate the fabrication of both structural and functional components, such as sensors, electronics, and drug delivery systems, is another promising direction. This comprehensive approach has the potential to result in the development of personalized, intelligent medical devices and implants that can monitor and respond to the

patient's physiological requirements. In general, the future of AM in the biomedical field appears promising, with the potential to transform the way we approach medical treatment, tissue regeneration, and personalized healthcare [26, 27, 32].

New frontiers in the biomedical field have been uncovered as a result of the research and technology development of AM. To address unmet clinical requirements, AM has evolved into a potent instrument, ranging from the production of patient-specific medical devices to the fabrication of intricate tissue scaffolds [27, 34, 36, 42]. Further advancements in metal AM through different levels of hybridization [43–44] and the integration of multi-axis kinematic systems [45] contribute to the fabrication of stress-free components with high geometric complexity.

9.7 CONCLUSIONS

In the medical field, AM is transformative, allowing for patient-specific prosthetics, implants, and surgical tools, supported by advancements in imaging technology like CT and MRI for accurate anatomical modeling. Compared to traditional manufacturing, AM is more efficient and cost-effective, particularly for low-volume, personalized medical devices. Biomedical AM materials are expanding to include biocompatible options such as hydrogels, supporting applications in tissue engineering and bioprinting. Despite challenges in biocompatibility and scalability, AM's integration with emerging technologies promises significant advancements in personalized healthcare and regenerative medicine.

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10 Industry 4.0 Interventions in Additive Manufacturing of Bio-Implants

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10.1 INTRODUCTION

Additive manufacturing (AM) is transforming the manufacturing landscape, impacting industries from automotive and aerospace to healthcare and defense [1–3]. While AM is a key Industry 4.0 technology, it is increasingly integrated with other advanced technologies such as big data, machine learning (ML), and artificial intelligence (AI). This synergy is particularly enhancing patient comfort, is cost-effective, achieves complex medical industry requirements, and streamlines the production of customized implants, prosthetics, and a variety of medical devices [4, 5]. By leveraging data-driven insights and automated processes, AM not only improves the precision and efficacy of healthcare manufacturing but also enables the design and development of highly personalized solutions that were previously difficult to attain. For instance, personalized 3D-printed titanium implants can be designed and manufactured using AI-driven algorithms with precision, offering superior anatomy, reduced surgery time, and faster heating compared to conventional implants.

The manufacturing of complex, customized bio-implants for patients would be near impossible or unaffordable using traditional approaches like injection molding, and CNC machining, and so AM, also called 3D printing, helps to the boundaries even further of bio-manufacturing with no to very less post-processing with the integration of other Industry 4.0 technologies. Although several benefits and disruptive applications of AM with the synergy of other Industry 4.0 technologies for bio-implants and other relevant applications, the literature is silent in enlisting the various Industry 4.0 technologies and their applications in the domain of healthcare. This research is one of the primitive attempts to explore various Industries 4.0 technologies with the synergy of AM for transforming healthcare, particularly in the area of prosthetics, implants, and medical devices.

10.2 OBJECTIVE AND METHODOLOGY

This research aims to demonstrate an extensive overview of the available scientific literature on the application of Industry 4.0 technologies with the integration of AM technology for bio-implants, prosthetics, and medical devices. To attain this, the study explores how AI, Internet of Things (IoT), Blockchain, Cyber-Physical Systems, and

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other technologies are combined with AM to strengthen the personalization, efficiency, and precision of bio-implants [4].

To achieve this objective, a systematic literature review was carried out to identify key research articles in this domain. Keywords utilized for this systematic review are "Industry 4.0 in bio-implants," "additive manufacturing," "AI in medical devices," and "IoT in bio-implants" and their synonyms. This methodology helps to identify the key contributing articles in the domain of Industry 4.0 and AM for implants, prosthetics etc. and future research direction.

10.3 CARRYING OUT THE LITERATURE REVIEW

At the outset, the authors gathered a list of scientific publications from various databases like Google Scholar and Scopus but restricted the articles to only English publications. Several keywords like "additive manufacturing," "Industry 4.0 Technologies," "Bio-implants," and relative terms were utilized to capture relevant studies in the search query. In the next stage, through the abstracts, the non-relevant articles were screened out as it is not within our scope. In the third stage, a full assessment is carried out, which results in qualifying all articles. Further, the scarcity of related academic papers on upcoming technologies in bio-implants motivates the authors to explore the white papers, market research reports, and allied documents to understand key technologies that transform bio-implant production, along with identifying gaps that provide opportunities for future research and development.

The content analysis of the systematic literature review is classified into four segments: Industry 4.0 in AM, type of AM technologies and their application in bio-implants, the role of Industry 4.0 and AM for application of bio-implants, prosthetics, and medical devices, and future outlook of bio-implants through the lens of Industry 4.0 technologies.

10.3.1 Industry 4.0 in Additive Manufacturing for Bio-Implants

In the field of bio-implants, prosthetics, and related applications, the integration of Industry 4.0 technologies with AM marks a significant paradigm shift. This unique combination leverages advancements like smart manufacturing, digital twins, AI, big data analytics, and the IoT to create data-driven, efficient, and interconnected environments that enhance manufacturing capabilities [5, 6]. Consider the example of IoT enabling a manufacturing facility that gathers real-time data monitoring of production, ultimately ensuring high accuracy and personalized bio-implant.

The use of ML, digital twins, big data, AI etc., to enhance implant design and development, is highly beneficial [7]. Through digital twins, the practitioners can simulate the digital replicas and their impact on patient outcomes, ultimately increasing the product development time while reducing the production cost and minimizing or sometimes eliminating the errors in the final implant or process [8]. This approach not only produces durable and biocompatible products but also helps ease stringent healthcare standards and certifications. Thus, Industry 4.0 and AM interventions not only elevate the implants and prosthetics manufacturing to the new highest, outperforming in efficiency and quality compared to the conventional options. More details

TABLE 10.1
Industry 4.0 Technologies, Additive Manufacturing Intervention in Bio-Implants Applications [4–9]

Technology	Application in Bio-Implants
Artificial intelligence (AI)	Optimizes bio-implant designs customized solutions for each patient and predicts surgical outcomes for increased precision.
Internet of Things (IoT)	Allows real-time monitoring of bio-implant functionality and patient health post-surgery by transmitting data from smart implants.
Blockchain	Helps ensure secure, traceable production processes, allowing for improved transparency and compliance in the bio-implant supply chain.
Big data and analytics	Allows the processing of enormous datasets for optimizing bio-implant designs, assessing risks, and enhancing personalization for patient-specific solutions.
Cyber-Physical Systems (CPS)	Connects physical bio-implants with digital models for real-time virtual testing and simulations before manufacturing.
Augmented reality (AR)	Helps surgeons by providing real-time visualization during procedures, enhancing precision and implant placement accuracy.
Machine learning (ML)	Analyzes past data from bio-implants to enhance further design processes, reducing failure rates and improving efficiency.
Cloud computing	Enables collaboration across global teams for designing bio-implants, manufacturing, and data sharing, allowing remote operations.
Digital twin technology	Forms a digital replica of bio-implants for ongoing monitoring, prediction-based maintenance, and post-surgery performance optimization.
3D printing (additive manufacturing)	Produces customized bio-implants with complex geometries, personalized features, and earlier turnaround times.
Robotics	Aids in automatized bio-implant manufacturing and precision-based surgical processes, which minimizes human error and improves efficiency.
Simulation	Simulates surgical procedures and placement of implants, decreasing risks and allowing for improved pre-operative planning and safety of patients.

about various Industry 4.0 technologies used for bio-implants, prosthetics, and relevant applications are given in Table 10.1.

10.3.2 Evolution of AM Materials

The evolution of material choices in AM for medical implants and prosthetics has progressed considerably, initiating with polymers and metals that offer foundational support in biocompatibility and structural integrity. In the early stage, the AM technology is compatible with popular materials like acrylonitrile butadiene styrene (ABS) and polylactic acid (PLA) due to the benefits of low cost, biocompatibility, and ease of fabrication [10]. However, these materials are limited to prototypes and non-load-bearing applications in assisting researchers and medical professionals in developing personalized models for educational purposes and surgical planning. Due to key constraints as discussed above, the research proposed to expand the new

material to outperform these limitations and precisely fulfill the customer requirements of prosthetics and medical implants.

In response to these limitations, new materials (medical grade polymers) have been introduced, like polyether ether ketone (PEEK), which offers superior mechanical properties, wear resistance, compatibility with medical image creation, and biocompatibility ultimately remains functional for extended periods [11].

In the last 15 years, substantial evolution has been taking place in metal AM materials like cobalt-chromium, stainless steel, and titanium alloys, that have become the cornerstone of prosthetics and implants due to superior mechanical properties like corrosion resistance, durability, tensile strength, and biocompatibility. Furthermore, due to the key benefits of AM, like patient-specific design and highly complex geometry fabrication, lightweight designs, porous structures (architecture of natural bone), better integration with natural tissue, and facilitating osseointegration, these materials are extensively utilized in the case of cranial and maxillofacial implants where precision and personalization were paramount [12, 13]. Particularly, cobalt-chromium is used for dental implants along with hip, knee prostheses, and fracture fixation plates and screws. Titanium is ideal for orthopedic implants like spinal cages and joint replacements due to its ability to bond with bones, while stainless steel is predominantly utilized for spine implants and joint replacements due to its high mechanical strength.

Ceramics play a distinctive role in AM in implants and prosthetics, especially in applications requiring bioactivity and high wear resistance. Ceramics like alumina (aluminum oxide) and zirconia (zirconium dioxide) are normally utilized for dental implants due to their long-term stability and bio-inert properties within the human body [14, 15]. Additionally, materials like hydroxyapatite, bioactive glass, and tricalcium phosphate are utilized for bone integration and regeneration, as they can precisely mimic the mineral composition of natural bone. Processes like binder jetting and powder bed fusion (PBF) allow for the creation of complex ceramic structures that are compatible with dental, orthopedic, and maxillofacial applications. The biocompatibility of these materials is necessary for supporting natural healing and minimizing body resistance risk.

Composite materials, such as carbon fiber-reinforced polymers, have been utilized in AM technology as a solution to achieve lightweight characteristics and strength in prosthetics [16]. These composites blend polymers with reinforcing agents like carbon fibers, enhancing their mechanical properties without adding excessive weight. In prosthetics, this combination allows for durable, high-performance limbs that offer better comfort and patient mobility. Additionally, composite materials are processed through various AM techniques, including material extrusion and photopolymerization, to create custom-fitted and aesthetically pleasing prosthetic solutions.

Natural biomaterials and emerging materials symbolize the frontier of AM technology in medical applications, particularly in regenerative medicine and tissue engineering. Natural materials like collagen, hyaluronic acid, cellulose, alginate, chitosan, and gelatin are assessed for their compatibility with human tissues and biodegradability [17]. These biomaterials are exceptionally beneficial in soft tissue engineering, where they promote healing and integration with the body. Emerging materials, such as graphene oxide, graphene, shape memory polymers, and hydrogels,

are also gaining traction due to their unique properties. For instance, graphene's electrical conductivity offers potential for implants with integrated sensors, while hydrogels can adapt to changes in body conditions, enhancing the functionality of prosthetic devices. These materials are paving the way for more advanced, patient-specific implants and prosthetics that respond dynamically to the human body.

10.3.3 Types of AM Technologies and Materials for Medical Implants and Prosthetics

Selecting appropriate AM technologies and materials for medical implants is essential to achieve the desired functionality, biocompatibility, and durability. Advances in AM have brought a diverse range of processes, each tailored to specific material types. As shown in the flowchart, materials are aligned with seven main AM technologies. The most commonly used vat photopolymerization is primarily employed for producing natural biomaterials such as cellulose, collagen, and gelatin, as well as emerging materials like hydrogels and graphene (and its oxide) [17]. However, these can also be manufactured using material extrusion technology.

In addition to these biomaterials, material extrusion is effective for producing natural compounds like chitosan, alginate, silk fibroin, and hyaluronic acid. It is also extensively applied in polymer fabrication, particularly for polyethylene, polymethyl methacrylate (PMMA), PEEK, and other synthetic polymers.

PBF and direct energy deposition (DED) are mainly employed for fabricating metal alloys such as titanium, 316L stainless steel, and cobalt-chromium [18]. These technologies are also commonly used for ceramic materials like alumina, zirconia, hydroxyapatite, tricalcium phosphate, and bioactive glass [19]. Additionally, PBF and DED are used for processing natural materials such as silk fibroin, composite materials like carbon fiber-reinforced polymers, and emerging materials such as bioactive glass and shape memory polymers (Figure 10.1).

10.3.4 Outlook of Implants and Prosthetics Industry through the Lens of AM Technologies

The medical implants and prosthetics industry is undergoing a significant transformation driven by the adoption of AM technologies. The integration of AM into healthcare, particularly in the production of personalized medical devices, is expected to grow substantially in the coming decade. Key drivers include the rising demand for patient-specific solutions, advancements in biocompatible materials, and the reduced cost of producing complex, custom implants.

According to recent projections, the use of AM in healthcare is expected to reach a market value of $78.06 billion by 2034 [20]. A major area of focus will be the development of biodegradable implants and bioresorbable scaffolds designed for tissue engineering and regenerative medicine. The materials then allow for potential temporary implants, which naturally dissolve once their functions end, leading to a reduction in the need for surgeries additionally and aids, especially in pediatric and trauma applications.

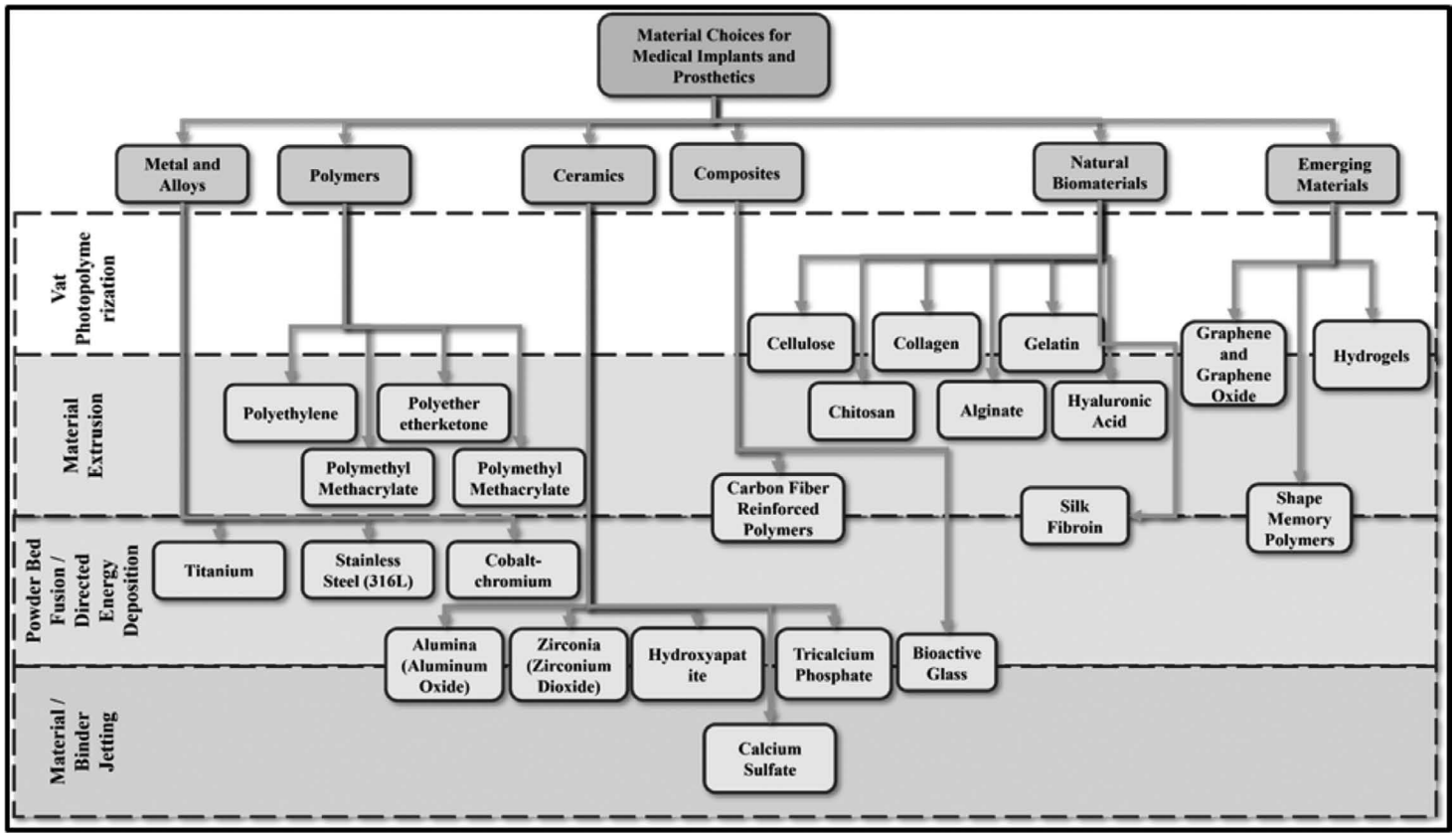

FIGURE 10.1 Material classification according to various AM technologies.

Approval of AM-produced medical devices by regulatory bodies like the FDA has been increasing, which facilitates wider adoption of AM technologies in mainstream clinical settings. The industry will see better integration of customized implants into everyday medical practice as and when the regulatory pathways become clearer.

The future of personalized healthcare can be represented by looking forward to innovative applications of AM, such as 3D bioprinting for creating tissue scaffolds and organ models. The combination and integration of manufacturing technologies with medicine have great potential to transform the way chronic diseases are treated and bring about customized and compatible solutions for patients globally. This advancement will improve the accuracy as well as the personalization of treatments.

10.3.5 Advance Material and Industry 4.0 Innovation for Bio-Implants

The evolution of material science is fundamental to the growing popularity of AM in the production of bio-implants. Industry 4.0 technologies play a crucial role in the discovery and application of advanced materials, such as biocompatible polymers and titanium alloys, which can be tailored to meet the unique needs of individual patients [9]. Designed to exhibit a high degree of compatibility with human tissues, the microstructures can be customized through the use of computational modeling and ML techniques and augmented reality (AR) to enhance the human tissue integration (body adoption), corrosion resistance, mechanical strength, and durability of these materials [21]. This, therefore, leads to improved osseointegration, offering tailor-made compatibility and improved long-term performance.

Furthermore, the integration of AM with nanotechnology drives innovation in bioactive implants by stimulating cell attachment and tissue integration, which significantly improves healing outcomes [9]. Another advancement in the direction of medical innovation is the 3D-printed sensor-embedded implants that can collect real-time patient health metrics data [8]. This further represents an advancement that promotes a holistic and personalized approach toward post-surgery monitoring, thereby enhancing functionality and promoting healing faster.

10.3.6 Quality Assurance and Compliance of Bio-Implants with Industry 4.0 Interventions

Ensuring high quality and stringent compliance standards is paramount in the domain of bio-implant production. Industry 4.0 technologies (which encompass automated inspection systems) significantly enhance implant quality through the utilization of sensors and advanced image analysis; this enables the early detection of defects [6]. This attitudinal change especially minimizes – and normally eliminates – waste and recalls, supplementing the simpler procedure of maintaining high standards of medical quality compliance at minimal costs. Moreover, these systems are efficient in collecting and interpreting real-time data which improves the metrics of the process control. Once again, while these are significant strides, these, in the long run, result in enhancement in the accuracy and precision of the products.

Also, Industry 4.0 enhances product compliance by improving the traceability of the products and providing digital information, such as 3D images of the objects

obtained by the technology of digital twins [22]. This is a critical feature that helps in satisfying the needs of the healthcare regulatory bodies as well as in promoting traceability of the product over the entire life cycle from conception to sale [8]. These advancements further allow manufacturers and users to facilitate compliance to intricate regulatory requirements thereby ensuring the bio-implants are effective and safe for patients.

10.4 DISCUSSION AND FUTURE RESEARCH DIRECTIONS

The bio-implant industry has transformed significantly, thanks to advancements in AM and Industry 4.0. These innovations have enabled the production of personalized, custom-designed bio-implants that can meet individual patient needs. AM technologies allow for the creation of complex geometries and intricate features that are difficult, if not impossible, to achieve with traditional manufacturing methods. With precise, custom-designed implants, patient outcomes are improving, and further advancements in bio-implant technology are emerging.

Today's bio-implant, prosthetics, and healthcare equipment industries emphasize mass customization, data-driven insights, informed decision-making, biocompatibility, and patient-centric solutions. Recent developments in AI, IoT, and Blockchain have made it easier to design, manufacture, and even monitor implant performance in real time after they are integrated into a patient's body [7]. AI aids in designing implants that perfectly suit and fit each patient, while IoT ensures implants remain functional before and after placement.

However, these advancements bring new challenges and research gaps, such as the need for more studies on the seamless integration, evaluation, and selection of suitable AM technologies for bio-implants, which require significant investment in training and infrastructure. A universally accepted standard for selecting AM technology is still lacking, complicating the establishment of implementation standards. There is a pressing need for a systematic framework that can help practitioners assess and choose AM technologies based on material properties, production capabilities, and patient benefits.

Data security is another critical challenge, as it pertains to both patient data and the intellectual property of proprietary products. Increasing digital connectivity raises the risk of cyber threats, underscoring the importance of robust cybersecurity. Additionally, while Industry 4.0 can reduce long-term manufacturing costs, high initial investments deter many small and medium-sized enterprises from adopting these technologies, thus slowing the full realization of Industry 4.0's potential in bio-implants and healthcare.

To address these challenges, government initiatives such as Industry 4.0 cluster development and the interconnection of Industry 4.0 service bureaus can promote adoption within the medical field. Future research should focus on how these technologies can improve the scalability and cost-effectiveness of personalized bio-implant production.

Further, in the context of AM and materials, the industry is transforming through the application of AM technology for medical implants and prosthetics by meeting personalized individual patient needs. Technologies like PBF,

material extrusion, and vat photopolymerization aid in the creation of customized implants to conform complex anatomical structures. These allow for improving implant fits and function, as well as reducing recovery time and complications, especially in fields like orthopedics, craniomaxillofacial surgery, and dental implants.

Companies like Stryker and Zimmer Biomet leverage AM to offer custom solutions using advanced materials like biocompatible metals, ceramics, and composites. They aid in innovations such as load-bearing implants and bioactive coatings that improve osseointegration. Although the field has been progressing, biodegradable implants and bioresorbable scaffolds represent promising future directions. However, challenges are still there in the selection of the most suitable AM technologies for certain implant types because current research lacks frameworks to guide these particular decisions.

The future research should also focus on addressing this particular gap by establishing clear criteria for AM technology selections on the basis of material properties, clinical needs, and patient-specific requirements. Evaluation of the biocompatibility of upcoming biomaterials, development of frameworks for the selection of processes, and understanding of the integration of multi-material systems for complex implants are included in the key research areas.

Moreover, it is important to investigate how the application of design for AM (DFAM) principles can enhance the integration of implants with bones and the development of designs that can be modified after surgery in order to advance personalized healthcare significantly.

The future of bio-implants hinges on advancements in DFAM, an emerging approach that leverages the unique capabilities of AM during implant design. In this context, it will be crucial to assess the functional and environmental impacts of bio-implants designed with DFAM principles. Additionally, the potential for simulation and AR in pre-operative planning presents a promising avenue to ensure optimal implant fit and integration within the body.

10.5 CONCLUSION

The objective of this research is to explore the impact of Industry 4.0 interventions on AM for creating bio-implants, prosthetics, and other healthcare devices. This systematic review highlights how AM, combined with Industry 4.0 technologies, has become crucial in enabling mass customization of bio-implants, providing precise and effective patient-specific solutions. Leveraging advancements like AI, IoT, digital twins, and other Industry 4.0 technologies facilitate faster production of bio-implants tailored to individual needs while offering real-time monitoring to ensure optimal outcomes for patients. Despite these advancements, further research is essential to develop a standardized framework for selecting appropriate AM technologies based on specific bio-implant requirements.

This review also helps to provide the foundation which outlines the list of materials and range of AM technologies to fabricate their application of medical implants and prosthetics through the conduction of a literature review. It highlights the shift from traditional materials such as metals to advanced polymers, composites, and

ceramics, showing how AM technologies like powder bed fusion, and vat photopolymerization, have transformed to enhance both biocompatibility and mechanical performance.

Future studies should also investigate the role of emerging technologies, such as ML and digital twin technology, in improving implant performance, modularity, and longevity. These also include the development of frameworks for matching materials with suitable AM technologies, exploring multi-material designs for specialized uses, and optimizing implant performance through DFAM principles. In summary, this chapter enhances the understanding of how Industry 4.0 technologies are revolutionizing the bio-implant sector and outlines key areas for future research, including technology selection, modular design, and real-time implant monitoring.

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11 Economic Implications of Additive Manufacturing in the Biomedical Industry

Anas Ullah Khan

11.1 INTRODUCTION

By now, it is well understood that 3D printing, or additive manufacturing (AM), has played a transformative role in the biomedical industry in recent years. From the development of synthetic scaffolds for supporting tissue growth to the fabrication of prosthetic limbs, titanium implants, and tools for planning complex surgeries, AM has significantly enhanced the quality of patient care. The adoption of these technologies across the global healthcare sector continues to grow, with their applications witnessing substantial progress. The global 3D printing healthcare market is expected to reach a staggering $4,070.8 million by 2027, according to a report published by Emergen Research [1]. However, the full potential of such technologies can only be realised when they are accessible and economically viable. The high cost of implementing certain innovations can limit their widespread adoption, despite their tremendous potential to improve patient outcomes.

Several opportunities and challenges shape the adoption of 3D printing technology in healthcare. The advances in technology have allowed the production of complex and customised medical devices, which meets the increasing demand for patient-specific solutions. Developing countries have also witnessed an increased demand for these facilities owing to rising income levels, the growing prevalence of life-threatening diseases, and population growth. In their efforts to enhance medical infrastructure and improve the quality of life for their citizens, these countries are actively adopting and promoting these innovative practices.

The challenges in the adoption of 3D printing technology in healthcare are related to the lack of awareness among healthcare professionals and patients. More efforts are required to bridge this gap by educating and spreading awareness. The healthcare sector is heavily regulated in most of the countries due to its direct dealing with its citizens' well-being. Therefore, any new technology or product needs to meet the required compliance guidelines before initial testing let alone getting absorbed in the hospitals. The cost is also a significant aspect of its implementation. AM minimises material waste significantly and accelerates the production cycles, which helps in reducing manufacturing cost. However, the initial cost, the ongoing costs associated with maintenance, and the need for skilled labour makes it a difficult decision to make. AM compensates for these costs in long term by incurring substantial savings, specifically in producing personalised implants, prosthetics, and medical devices

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where conventional manufacturing techniques incur higher costs due to less flexibility. Despite these challenges, the value added by the 3D printing technologies in healthcare is attracting the patients and the healthcare providers resulting in increasing adoption in many hospitals.

From the view point of economic implementation, scalability is a factor which could play an important role in decision-making. Since in biomedical sector, most of the requirements are related to bespoke medical devices, the AM provides the appropriate solutions as it is known for batch production. The entry of many low-cost printers in market also enables mass production, although it may not always be required or cost-effective in the healthcare sector. AM also plays a significant role in redesigning the delivery and supply chains of healthcare. AM helps in localised production of products, which reduces dependency on global supply chain and reduces the risk of distribution interruptions in the cases of emergency. The details of the products required for the patients could be easily shared across devices, which reduces the wait times for the patient to receive the treatment. This kind of production devolution from central factories to local healthcare providers or point-of-care (PoC) settings could definitely lead to more efficient and faster system. The latest research outcomes are also easier to integrate in case of AM.

This chapter examines the advantages and disadvantages of different economic factors, focussing on how AM is driving innovation in biomedical applications. It also looks at the new economic opportunities and challenges that could impact the future of healthcare delivery.

11.2 COST STRUCTURE OF ADDITIVE MANUFACTURING IN BIOMEDICAL APPLICATIONS

11.2.1 Equipment and Material Costs

The cost structure for AM in biomedical applications is largely affected by the high initial cost of AM setups, which could be even more significant for medical-grade machines (Figure 11.1).

The setups for processes such as direct metal laser sintering (DMLS) which could process biocompatible metals, such as titanium alloys, range between $300,000 and $1,000,000. Also, stereolithography (SLA) printers which are widely used for dental and orthopaedic applications are relatively less expensive costing from $5,000 to $100,000. The cost varies greatly due to the dimensional accuracy, minimum feature size (resolution), build volume, and accessibility. The material used in biomedical industry could also be quite expensive depending on the requirements. Many unique and specialised materials are used for applications such as tissue engineering, drug delivery, implants and prosthetics. The hydrogels used in tissue engineering, such as Alginate, Chitosan, Pluronic F127, and PEG (polyethylene glycol), cost around few hundreds of dollars. Alginate is available in cheaper prices due to its abundance in nature and simple extraction process but has limited cell-adhesion capabilities. Gelatin is also relatively cheap; however, it requires stabilisation to enhance strength. PEG is used for its wide scope in properties, but its synthesis may make it expensive. Pluronic could range up to $600/kg due to high purity requirement. Overall, the

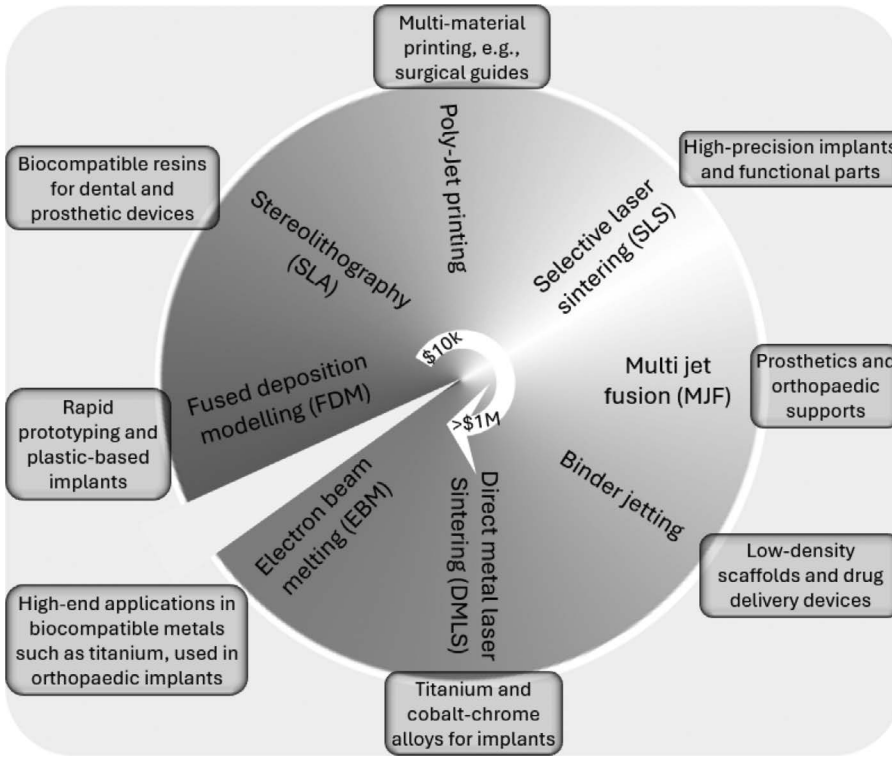
Multi-material printing, e.g., surgical guides
Poly-Jet printing
High-precision implants and functional parts
Biocompatible resins for dental and prosthetic devices
Stereolithography (SLA)
Selective laser sintering (SLS)
$10k
Multi jet fusion (MJF)
Prosthetics and orthopaedic supports
Fused deposition modelling (FDM)
Rapid prototyping and plastic-based implants
>$1M
Binder jetting
Electron beam melting (EBM)
Direct metal laser Sintering (DMLS)
Low-density scaffolds and drug delivery devices
High-end applications in biocompatible metals such as titanium, used in orthopaedic implants
Titanium and cobalt-chrome alloys for implants

FIGURE 11.1 AM processes costs and their main applications.

hydrogels are cost-effective and easy to use for research purposes. However, their scaling for specific applications might prove to be expensive.

Medical implants and prosthetics are generally made of titanium alloys, polyether ether ketone (PEEK), ceramics, and others. Their cost also lies in the same range of few hundreds of dollars. Ti-6Al-4V may cost around $300–$500/kg due to expensive gas atomisation process involved in its production. However, its high biocompatibility and durability makes it a good candidate for making implants. PEEK also costs in the similar range and provides good mechanical and thermal properties justifying its cost. Ceramics such as hydroxyapatite cost relatively cheaper and are widely used for bone integration. Although these implants and prosthetics materials require high initial investment, their longevity and performance make up for it.

The bioprinting of organs and vascular structures utilises collagen, custom bioinks, and nanocellulose. Collagen is an important component for organ scaffolds and might cost around $300–$500/kg. The custom inks might range from $500 to $1,000/kg depending on the degree of customisation and sterility requirements. Apart from the machines and raw materials, the biomedical AM setup also requires supplementary equipment for post-processing. Heat treatment furnaces and CNC (computer numerical control) machines for surface finishing are the most common methods, which can increase the total expenditure further.

11.2.2 Operating and Maintenance Costs

When considering the total cost of AM, several key factors related to its operation and maintenance must not be undermined. These are discussed as follows:

Energy consumption: The operating cost of AM machines should not be undermined, as some of the processes for metal deposition could involve high energy consumption. Processes, such as DMLS, may consume 2–4 kW, on the other hand we have low consumption processes such as SLA, which require around 100–300 W.

Labour costs: Since the AM process operation involves CAD (computer-aided design) designing, process monitoring, and post-processing, it needs highly skilled engineers and experts. However, it should also be noted that the number of workforce requirement is generally lesser than the traditional machining operations.

Maintenance: AM machines might need periodic calibration, part replacement, and cleaning, which could also add to the total cost. The annual maintenance cost for these systems could range from $10,000 to $50,000 depending on the operating hours and quality requirements. SLA systems incur lower maintenance costs, but the replacement of resin vats and laser modules could still be significant.

Software: Advanced AM systems require expensive software for topology optimisation, part slicing, and machine control. Licencing fees for such software, like Materialise or Autodesk Netfabb, can cost $1,000–$20,000 per year, further impacting operational budgets.

Overall, it could be said that for batch production or personalised part fabrication, AM provides a competitive cost; however, for mass production, the cost remains higher due to slower build rate.

11.2.3 Material Utilisation and Waste Reduction

Most of the AM processes for biomedical applications show very good material utilisation and reusability (Table 11.1). This helps in significant waste reduction compared to conventional machining processes where the losses might be as high as 50%. The implications of cost become more pronounced when using expensive biocompatible materials. Titanium powder recycling in AM can save up to 30% on raw material costs over time. Furthermore, reduced waste translates into environmental benefits, such as lower energy demand for material extraction and waste disposal, making AM a sustainable option for the biomedical industry.

Another very critical benefit of AM is realised through the use of lattice structures which optimise the material use while providing the required strength. These designs are almost impossible to fabricate using traditional processes, further stressing on the cost-effectiveness of AM for biomedical applications.

High initial capital expenditures for setups and equipment, relatively high material costs owing to the strict requirements for biocompatible materials, and ongoing

TABLE 11.1
Material Utilisation Aspects of Additive Manufacturing Processes for Biomedical Applications

Process	Material Utilisation Efficiency	Reusability	Common Raw Materials	Approximate Material Cost
Extrusion bioprinting	High (>90%)	Yes (sterility has to be maintained)	Hydrogel-based bioinks (e.g., alginate, gelatin)	$200–$400/l
Laser-assisted bioprinting (LAB)	High (~85–95%)	No, material degrades during exposure	Collagen, fibrinogen-based hydrogels	$250–$600/l
Inkjet bioprinting	Moderate (~70–80%)	Limited, due to contamination risks	Low-viscosity bioinks, cell suspensions	$150–$350/l
Stereolithography (SLA)	Moderate to High (~75–90%)	Yes	Photocurable resins (e.g., PEG-diacrylate)	$350–$900/l
Microextrusion bioprinting	Very high (>95%)	Yes (bioink sterility has to be crucial)	Composite bioinks with cells and scaffolds	$300–$700/l
Drop-on-demand bioprinting	Low to moderate (~50–70%)	Limited, due to contamination issues	Low-viscosity bioinks with suspended cells	$150–$300/l

operating costs, including labour, energy, and maintenance, could all be considered characteristics of the cost structure of AM in biomedical applications. However, AM offers a strong value proposition for high-value, customised biomedical applications due to its effective material usage and capacity to create complicated geometries with minimal waste. Although AM is not yet cost-competitive for large-scale manufacturing, its technological and financial advantages make it essential for use in several important applications.

11.3 ECONOMIC BENEFITS OF CUSTOMISATION AND PERSONALISATION

11.3.1 Reduced Design-to-Production Time

Titanium implant production using traditional methods requires extensive mould preparation and machining. The AM directly translates the design into physical parts, without using tooling and setup requirement. This results in reduced lead times and enhances responsiveness to patient needs by allowing manufacturers to react immediately to medical emergencies. It could be better understood from Figure 11.2. Since fewer intermediate prototypes are required, the time savings also affect the cost of product development. As AM allows for quick design iterations and on-demand production without the delays caused by tooling changes, studies show that it can reduce product development timelines by 40–50% in some situations. In the biomedical industry, where delays can have huge financial and human consequences, time efficiency is crucial. A McKinsey analysis claims that the economic

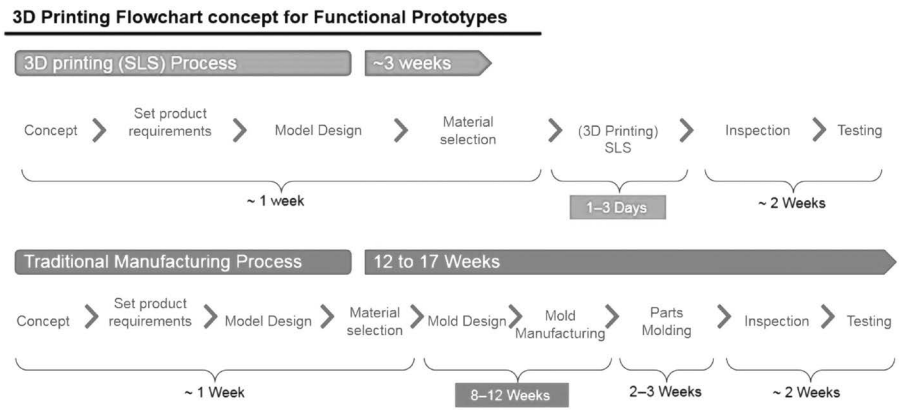

FIGURE 11.2 Chart flow from Windform website, case study: Successful use of PBF professional 3D printing and high-performance composite material in the manufacturing of airbag housing container.

Courtesy of CRP Technology, image provided by Joyson Safety Systems.

benefit of AM in reducing medical device time-to-market might result in billions of dollars in savings worldwide, especially for expensive, low-volume products. In regulatory-driven industries like healthcare, where compliance frequently necessitates numerous design iterations before approval is obtained, the reduced time-to-market benefit is amplified.

11.3.2 Enhanced Fit and Functionality

AM Devices with improved fit and functioning provide patient-specific fits. By reducing the probability of postoperative problems and the necessity for corrective operations, customisation improves clinical outcomes and results in significant cost savings. For example, hearing aids made with AM methods such as SLS are customised to fit patient's ear canal, improving comfort and sound quality while lowering the frequency of changes and replacements. Since fewer complications translate into lower hospitalisation rates and related expenses, the economic effects also include less strain on the healthcare system. Incorrect execution or misalignment of complex surgical procedures, such as cranial reconstructive implants, may need thousands of dollars in correction surgeries. A better fit speeds up patient recovery, which indirectly boosts the economy by lowering insurance obligations and increasing worker productivity. An additional noteworthy benefit is the incorporation of porous structures or functional gradients into implants, which are not possible with conventional production. These designs enhance bone lifespan and integration, which further lowers patients' lifelong medical expenses.

11.3.3 Implication for Mass Production

One of the most revolutionary economic prospects made possible by AM is mass customisation. AM can create distinctive components at a price similar to that of

regulated parts, in contrast to traditional manufacturing, where economies of scale depend on creating identical goods. The expansion of the manufacturing of medical devices such as prosthetics, orthotics, and hearing aids will be significantly impacted by this paradigm change.

Due to AM's unmatched capacity for handling high-volume customisation, 98% of in-ear hearing aids produced worldwide are currently made utilising this technology. Leveraging developments in digital workflows, such as batch production systems and artificial intelligence (AI)-assisted design automation, allows for scalability. The cost-effectiveness of mass customisation is driven by economies of scope rather than scale because a single manufacturing setup can accommodate a large number of designs without retooling. The ability of AM to minimise waste further boosts its economic potential. For instance, compared to roughly 50% in conventional machining techniques, material utilisation rates of up to 95% are achieved when implants are produced utilising powder-based AM technologies such as electron beam melting (EBM). The cost of producing high-value products using expensive materials like titanium or cobalt-chrome alloys is greatly decreased by this high material efficiency.

AM is being used by business models such as distributed manufacturing networks to scale customisation while keeping costs low. Hospitals or regional facilities employing AM equipment could manufacture implants and prosthetics locally rather than in centralised factories, reducing lead times and transportation expenses. In disadvantaged markets, where accessibility is still a problem, such decentralised arrangements are especially advantageous. NIST estimates that the medical and dental industry in the United States alone made $367 million in 2013 from AM, with a compound annual growth rate of more than 20% anticipated. This expansion is a result of the growing viability of AM for low-cost, high-volume healthcare customisation.

11.4 SUPPLY CHAIN TRANSFORMATION AND LOGISTICAL COST SAVINGS IN THE BIOMEDICAL INDUSTRY THROUGH ADDITIVE MANUFACTURING (AM)

11.4.1 On-Demand Production

One of the most prominent advantages of AM is its ability to enable on-demand production, that significantly affects the supply chain dynamics. While the conventional approaches rely on an extensive inventory storage, AM eliminates this need, as the items are manufactured only when required. Biomedical sector applications have products with very short shelf lives, high customisation requirements, and standard sterilisation requirements, which demands such models as provided by AM. Since AM helps in shifting the production from large-scale batch production to a produce-on-demand strategy, it substantially reduces if not eliminates, the warehouse and large inventory costs. These strategies have shown their true potential during the COVID-19 pandemic, when AM was utilised to address the shortage of medical supplies, such as mask filter adapters and ventilator components (Figure 11.3) [2]. During this pandemic, due to a delay in global supply chains, the Food and Drug

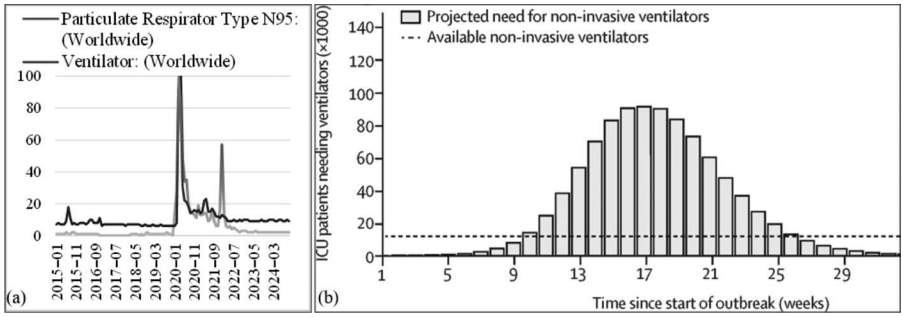

FIGURE 11.3 (a) Keyword search for 'Particulate Respirator type n95 mask', and 'ventilator' shows sudden rise during emergency situations, and (b) projected number of ICU patients requiring ventilators in the absence of any community interventions with $R_0 = 2{\cdot}5$ [4].

Administration (FDA) issued a memorandum of understanding (MoU) between National Institutes of Health (NIH), Veterans Health Administration (VHA), and FDA. The goal of this public-private partnership was to accelerate information-sharing and production of additively manufactured products to meet the urgent public health requirement. The shared prototypes were tested, reviewed, and approved and the final products were made available on their website [3]. This example highlights the impact of 3D printing on production strategies. It assists in decentralising manufacturing, which allows localised production followed by quick distribution. The flexibility of customisation is key for catering to a vast and diverged patient demographic, allowing medical equipment to be adapted to unique needs and specifications, thereby enhancing efficacy and care quality.

11.4.2 Decentralised Manufacturing

Decentralised manufacturing makes it possible to produce medical devices and products in close vicinity to the healthcare facility. The faster delivery resulting from reduced dependency on long and complex transportation networks also helps in cost-reduction. These types of localised production centres significantly enhance the response time to meet the changing needs over time or in emergencies. It also plays a significant role shrinking the environmental impact of logistics which is considered a massive factor for global carbon dioxide emissions. According to European Environment Agency, the share of logistics responsible for these emissions may rise up to 40% by 2050 [5].

Some of the research like by APQC suggest that centralised manufacturing is around 3% cost-effective than the decentralised manufacturing. However, it is very unlikely to be the case with respect to biomedical industry, as 3D printing introduces some distinct advantages. In biomedical applications, the implants, tools, prosthetics are heavily dependent on the patient and the variability is unlike any other industry. The centralised manufacturing, where the supply chain, machines, and tooling are almost rigid, and therefore it could not compete with the decentralised manufacturing in this scenario. Moreover, 3D printing also reduces significant material that also leads to cost cutting.

11.4.3 Case Study: Role of Additive Manufacturing in Rerouting Supply Chains

In 2017, the Caribbean was hit by the hurricanes Irma and Maria which was considered one of the most catastrophic events in the history of Atlantic hurricanes. The hurricanes devastated Puerto Rico along with ten other countries disrupting countless of lives and ruining infrastructure. Close to 1,000 people were killed in Puerto Rico and only 20% of the island was left with functional services. The power outages and shortage of medical supplies grappled the hospitals further worsening the crisis. Essential items such as food, water, shelter, and other non-food items became acute.

In this situation, 3D printing emerged as a transformative technology to compensate for the interrupted traditional supply chains. Non-profit organisations such as Field Ready played a huge role by showcasing the rapid and localised manufacturing of critical supplies. The conventional disaster relief supply chains were plagued by mediators and inadequacies and often failed to deliver help on time. The proposed model by Field Ready focussed on precision in fulfilling the need of the distressed communities and promoted knowledge sharing and trained local responders to use the technology. Their team consisted experts from varied fields such as engineering, management, and designing, and they worked together with the healthcare practitioners. They designed and fabricated various medical disposables and other components on-site. They also designed and fabricated a replacement pipe fitting using the portable 3D printers to repair damaged pipes. Their main methodology was to create comprehensive kits containing all relevant information such as design files, templates, and instructions to enable more unskilled people to use the technology effortlessly.

The deployment of 3D printing also faced several setbacks on the field. The printers had to justify their feasibility and cost investment by producing more parts in lesser time. The multitude of challenges created the requirement to modify designs frequently and required trained workforce. Since the electrical supply was seriously hit in several regions, 3D printing operations were further challenged. This highlighted the need for alternate energy solutions such as solar power to keep the printers operation in off-grid regions. Continuous innovations in 3D printing technology are therefore required keeping in mind the disaster situations. The latest developments keep on enhancing part strength, broadening the material library, and reducing the printing time. These innovations are believed to further solidify the role of this technology in such emergency situations where the traditional methods of relief suffer.

Earlier during 2010 Haiti earthquake also, 3D printing played a great role in disaster relief. Dara Dotz, who was a pioneer to utilise 3D printing in humanitarian aid, established iLab Haiti to counter the devastation of the earthquake [6]. She also collaborated with Field Ready and Made in Space to reroute supply chains. Field Ready collaborated with local personnel to fabricate medical disposables, recycle plastic filament, and deliver on-site solutions using MakerBot 3D printer. Similar schemes have been implemented in countries like Kenya and Jordan, tackling various challenges such as fabricating prosthetic limb and manufacturing pipe clamp.

All these efforts highlight the true latent of 3D printing in emergency requirements. It enables hyper-local fabrication and limits disruption caused by the traditional supply chains and thus offers a swift and efficient way to tackle emergency.

11.5 REGULATORY AND QUALITY ASSURANCE COSTS

11.5.1 Compliance and Certification Expenses

Compliance and certification costs embody a substantial portion of the economic burden in the AM of biomedical devices. Regulatory bodies such as the FDA and ISO obligate stringent criteria to ensure safety, efficacy, and quality in products designed for medical applications (Table 11.2). These requirements include the following:

Material characterisation and biocompatibility testing: Standards such as ISO 10993 have laid out several regulations and guidelines for AM-produced medical devices to pass through rigorous material characterisation and biocompatibility testing. These tests comprising physicochemical analyses, toxicological evaluations of leachable, hemocompatibility testing and several others biocompatibility analysis ensure suitability for medical applications. These tests require the use of sophisticated and specialised equipment, making them expensive which subtly rattle the economics of AM in biomedical industry.

Devices standards: The devices fabricated with the help of AM should meet the desired performance and safety criteria according to their category. For example, devices such as a blood glucose meter or orthopaedic implants have to be compliant with ISO 13485 which governs quality management for medical devices to ensure safety and reliability. These certifications need detailed audits, documentation, and operational adjustments, further exacerbating the overall costs [7].

FDA approval pathways: In countries such as the United States, the AM devices follow the 510(k) premarket notification or sometimes even more in-depth premarket approval (PMA) process. Overall, 510(k) applications and associated testing costs are estimated at $20,000–$30,000 while the PMA may range from $300,000 to more than $1,000,000. PMA also includes clinical trials and other additional testing.

Post-market supervision: Manufacturers are obligated to maintain tools for post-market surveillance and case reports. Advanced tracking and maintenance systems might be required for these activities, further adding to the expenses.

Sterilisation and packaging: ISO 11607 and related standards mandate validation studies for sterilisation processes and packaging stability. Accelerated ageing tests and transport simulations with associated costs of tens of thousands of dollars per product are also an integral part of the compliance process.

All these variety of compliance requirements outspread product development timeline and require huge upfront investment, which poses significant challenges for small and medium enterprises.

TABLE 11.2
The Regulatory Authorities Responsible for the Guidelines on Additive Manufacturing Technologies for Biomedical Industries

Regulatory Authorities	Notable Regulatory Framework	Focus	Relevance to AM
Food and Drug Administration (FDA), 1906 *Headquarter*: United States *Jurisdiction*: United States	21 CFR (Code of Federal Regulations), FD&C Act	Food and drugs	Ensures the safety and efficacy of additive-manufactured medical devices by providing guidance on various aspects ranging from design to final product implementation; guidelines on software workflow, material controls, post-processing, process validation, device testing considerations, mechanical testing, dimensional measurements, material characterisation, material residues, and sterilisation; provides guidelines on minimum possible feature size, machine tolerances, imaging techniques, cybersecurity for patient-matched devices, and patient identifier; biocompatibility guidelines according to ISO-10993 standards
Medicines and Healthcare products Regulatory Agency (MHRA), 2003 *Headquarter*: United Kingdom *Jurisdiction*: United Kingdom	UK MDR 2002	Medicines, medical devices, and blood components for transfusion	Guidance and regulations for 3D-printed medical devices and personal protective equipment (PPE) during the COVID-19 pandemic; classification of products, conformity assessments, and the necessary safety and performance standards; risk management, technical requirements, biological safety, and sterilisation processes for 3D-printed medical device [8]
European Medicines Agency (EMA), 1995 *Headquarter*: The Netherlands *Jurisdiction*: European Union	REGULATION (EU) 2017/745	Regulation on clinical investigation and smooth functioning of medical devices market	Regulatory requirements for custom-made devices; Technical documentation for custom-made devices, including design, manufacturing processes, and materials used; ensuring quality management system in accordance with ISO 13485; post-market surveillance to monitor the safety and performance of custom-made devices [9]

(Continued)

TABLE 11.2 *(Continued)*
The Regulatory Authorities Responsible for the Guidelines on Additive Manufacturing Technologies for Biomedical Industries

Regulatory Authorities	Notable Regulatory Framework	Focus	Relevance to AM
ISO (International Organisation for Standardisation), 1947 *Headquarter*: Switzerland *Jurisdiction*: Global	ISO 13485 (Medical Devices Quality Management)	Diverse, including climate change, healthcare, quality management, and artificial intelligence	Highly relevant to additive manufacturing (3D printing) in the medical device industry; Develops AM standards and safety protocols for entire production process, including design, risk management, documentation, and continuous improvement practices
Therapeutic Goods Administration (TGA), 1989 *Headquarter*: Australia *Jurisdiction*: Australia	Therapeutic Goods Act and Regulations	Medicines, medical devices, diagnostic tests	Evaluate material chemistry and biocompatibility; Regulations for cleaning of non-sterile devices; EN556 for a Sterility Assurance Level [10]
China National Medical Products Administration (NMPA), 2018 *Headquarter*: China *Jurisdiction*: China	Drug Administration Law	Drugs, medical devices, cosmetics	Approved devices such as additive-manufactured polyether ether ketone skull defect repair prosthesis, and additive-manufactured customised knee joint prosthesis; implantable bone, joint, oral hard tissue, acetabular cup, vertebral body, and patient-matching mandibular prosthesis. It also includes a technical guideline for custom bone implants and supporting tools [11, 12]

11.5.2 Quality Control in AM

Quality control in AM for the biomedical industry involves diverse and complex processes that follow critical safety protocols due to the high stakes of patient safety and life. Some of the costs associated with quality control are as follows:

Real-time monitoring systems: Real-time process monitoring is increasingly required to ensure defect-free AM fabrication. Expensive sensors and monitoring techniques such as optical coherence tomography (OCT), thermal imaging, laser scanning, and radiography are utilised to monitor AM process characteristics, including bead geometry, interlayer temperature, voids, and surface quality. The cost of these systems ranges from $50,000 to $200,000 per unit [13].

Post-processing requirements: Post-processing methods, such as surface polishing, heat treatment, and sterilisation, are some of the standards considered important to meet the regulatory guidelines. These processes alone could account for up to 30% of the total fabrication cost.

Validation: Regulatory bodies require exhaustive validation of AM processes, including mechanical testing, dimensional accuracy, and material property characterisation. This compels for substantial investment in concerned equipment and skilled workforce.

Data analytics: The integration of data-driven approaches, such as data analytics and machine learning in quality control, is garnering interest to predict and eliminate defects. Software development and other implementation investments have to be kept in mind regarding this.

Fabrication failures: AM processes are dependent on several process parameters and sometimes environmental conditions and slight deviations could lead to porosity and warping defects. Optimisation of process parameters is associated with costly destructive testing and multiple iterations to establish the process.

Training: The advanced technology associated with AM necessitates skilled personnel proficient in material characterisation, sophisticated machine operation, and data analysis, thereby increasing human resource costs.

Quality control measures are indispensable in ensuring patient safety and regulatory compliance; however, they greatly influence the economics of biomedical AM products. By identifying more effective methods to reduce these costs, manufacturers can enhance overall efficiency and decrease time-to-market. Common testing facilities may lower testing and certification expenses through economies of scale. Additionally, government support in the form of subsidies and basic training could encourage small and medium enterprises.

11.6 LONG-TERM ECONOMIC IMPACT ON THE HEALTHCARE SYSTEM

11.6.1 Cost-Efficiency in Patient Care

AM enables the production of personalised implants and devices providing several advantages. These custom services often improve the surgical outcomes, reduce complications, and fewer follow-up routines, eventually reducing the healthcare expenses. The conventionally used implants might require adjustments prior to surgery to accommodate the specific anatomical requirements of the patient. These additional interferences might increase the risk of complications during and after the surgery. On the other hand, personalised implants are designed based on patient anatomy need, resulting in better fit and reducing the possibilities of re-surgery (Figure 11.4) [14].

AM also improves production processes by minimising material waste. This becomes significant for expensive biocompatible materials such as titanium and cobalt-chromium alloys. Moreover, PoC manufacturing in hospitals, equipped with

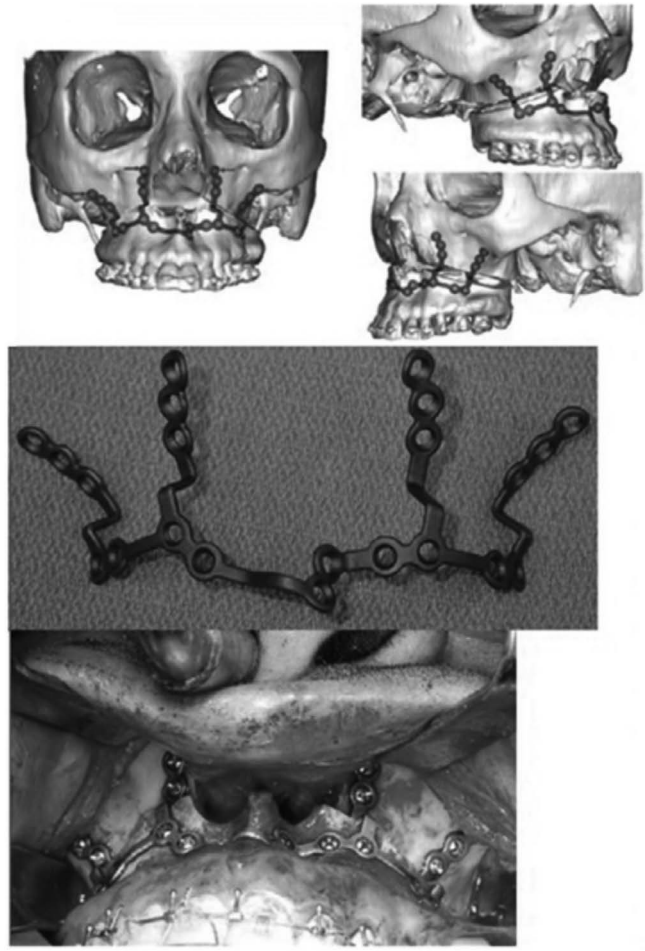

FIGURE 11.4 Patient-specific implant (PSI) made possible due to 3D printing [15].

AM facilities, allows on-site fabrication of implants and other devices, reducing transportation time and costs. These factors reduce manufacturing cost and help in faster completion times.

11.6.2 Potential for Reduced Healthcare Costs with Early Intervention

Immediate and subsequent effective treatments are made attainable by AM's quick fabrication of bespoke healthcare supplies. Pre-operative prototypes and 3D-printed surgical guides, for example, assist doctors to strategically prepare and conduct surgeries with greater precision, cutting down on procedure duration and related expenses. Additionally, faster treatments reduce the chance of complications, which shortens stay in hospital and recuperation periods for patients. Furthermore, medical conditions could be dealt before they worsen by utilising AM's expertise with earlier

identification and customised treatment strategies. Bespoke orthopaedic implants, for instance, may prevent long-term joint deterioration, limiting the need for expensive surgeries and minimising ongoing expenditures on healthcare.

11.6.3 Insurance and Reimbursement

Despite its many benefits, insurance and reimbursement procedures bring serious obstacles to AM's broad use in the biomedical industry. Even though customised implants provide long-term savings, many insurance plans are not yet set up to cover the higher initial expenses. There is a variance in the reimbursement policies between custom and standard devices. Custom implants, such as those used in orthopaedics or cranial reconstruction, lack standardised billing codes and, therefore, face reimbursement delays or partial coverage due to their higher cost. For example, patients opting for patient-specific instrumentation (PSI) used in joint replacement are not always reimbursed at the same rate as their standard alternatives (the indirect cost of patient-specific instruments). To counter this, companies like Smith & Nephew's LEGION® are adopting hybrid models and fabricating semi-custom implants that attempt to keep the benefits of customisation with manufacturing cost lower than fully customised products. These hybrid models improve the clinical outcomes and make the devices more cost-effective for healthcare firms and insurers. The reimbursement policies need to be revised and should aim for more flexible coding structures that better reflect the cost and clinical benefits of innovative devices and technologies.

11.7 OUTLOOK FOR ADDITIVE MANUFACTURING IN THE BIOMEDICAL INDUSTRY

The extensive research in material science is likely to enable the production of more complex human organs, potentially advancing healthcare to cure and treat conditions that are currently considered impossible to address. Continued research would help in diversifying the portfolio for approved biocompatible materials. The ongoing research is also focussed on scaling the production of biocompatible materials which could reduce cost. The integration of AI-driven process optimisation tools could lead to further reductions in machine idle time, material waste, and overall production costs. Many market reports estimate that the cost-per-part for many AM techniques would soon match or even surpass traditional manufacturing methods for customised biomedical devices. This would make AM a primary choice for many applications.

Technological advancements, such as generative design, in-situ monitoring, and digital twins, are already enhancing AM processes. Generative design is being utilised for lattice structures in implants to reduce weight and gain high strength. Digital twins enable real-time virtualisation of manufacturing setups, reducing iterations in prototyping. Companies like Boston Scientific have already started using in-situ monitoring to ensure precision in stent fabrication, and it could be extended to more complex biomedical devices.

AM has already demonstrated its significance in sustainability, and recent reports estimate that it will further enhance this by making material waste almost negligible

and significantly reducing transportation emissions through the promotion of localised production. GE additive have been able to reduce the raw material cost of titanium implants by ~35% by adopting AM.

Future advancements seek to address regulatory challenges, particularly related to traceability and consistency. Researchers are focussing on blockchain for secure records and AI for defect detection. Siemens' centralised digital platforms have already made the compliance processes easier for companies producing patient-specific implants. The regulatory bodies are expected to establish detailed and comprehensive guidelines and make the approval process fast and cost-effective. It would definitely encourage more enterprises to enter biomedical industry and provide a diversity in products and services. Industrial training programmes and inclusion of AM in biomedical engineering curriculum are expected to bridge the gap of lagging skilled workforce.

All these factors shape a very promising future for AM in biomedical industry and the experts believe the soon AM would become a standard manufacturing method for personalised medical devices. The future of AM in the biomedical industry is outlined by its capacity to lower costs, enhance precision, and promote sustainability. As technology matures and regulatory frameworks expand, AM is destined to reveal unique opportunities, driving both economic and medical developments.

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